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Editorial

Reflections on Etiology of Heart Disease

IN OUR modern attempts to classify the etiology of heart disease in a cut and dry fashion, we overlook a great many factors which enter into the complex mechanism of the causation of disease. Although some diseased states of the heart may be definitely traceable to specific extrinsic factors such as bacterial, spirochetal and parasitic infestations, to chemical and drug intoxication and to severe trauma, these constitute a comparatively small percentage of cases of cardiac disease. The vast majority of cases are caused by such constitutional diseases as arteriosclerosis and hypertension. Other much less frequent forms of constitutional disturbances that may affect the heart are neurogenic, blood dyscrasias, metabolic, endocrine, pulmonary, neoplastic, callagen and congenital maldevelopment.

All these conditions which we are tempted to classify as intrinsic causes of heart disease are not truly primary causes. To take for example, arteriosclerotic and hypertensive heart disease, we can hardly consider arteriosclerosis and hypertension primary causes. They are merely to be looked at as diseased constitutional states which may produce structural changes in the heart as well as in other organs or structures of the body. In other words, whatever the causes may be that produce arteriosclerotic and hypertensive heart disease they are those that produce arteriosclerosis and hypertension, and they are still far from solved. To label these forms of heart disease as being caused by arteriosclerosis and hypertension is therefore to admit our ignorance of the etiology.

The present-day concentration on laboratory methods of study of these diseased states we believe will not entirely solve the problem. Blood lipid studies, the effect of sex hormones and other chemical studies in arteriosclerosis admittedly throw some light on the subject but do not clarify the underlying etiology. Also, disregarding the well established causes of some forms of hypertension, such as the various kinds of renal disease, uncomplicated thyrotoxicosis, aortic insufficiency, loss of arterial elasticity as age progresses, and others, the causes of the vast majority of cases known as essential hypertension are still shrouded in mystery. That the underlying factor is an increase in the peripheral resistance to the arterial blood flow caused by constriction of the arterioles has been established. What brings about persistent or intermittent constriction of the arterioles, however, is not known. Neurogenic and psychogenic factors, some endocrine disturbances, electrolytic imbalance, reaction of a pseudoglobulin in the blood with renin forming angiotonin which has a constricting effect on the blood vessels, and many other theories have been advanced, but none of these has been definitely proved.

The observations[1] that arteriosclerotic and hypertensive heart disease, particularly the former, are prevalent in areas where the mo-

mentum of life is increased, where industrialization is more highly developed and where there is a greater tendency for populations to concentrate in urban areas would tend to substantiate the theory that some factors incident to mode of living and activity under such conditions may enter into the etiology of these diseases.

In an attempt to establish the causes of the various underlying constitutional diseases we must concentrate more attention on the study of various factors that may play a role in modifying the hemodynamics of the circulation and the physico-chemical state of the individual. Heredity is undoubtedly one factor. Other factors to be considered are various environmental conditions such as climate, mode of living, the extreme nervous tensions of our modern civilization, the overindulgence in food, alcohol and tobacco on the one hand, and the undernutrition and poor hygienic environment of the underprivileged on the other hand, insufficient rest, relaxation and open air life and activity of city dwellers, and many other factors that may have influence on the cellular behavior of the human body. All these should be studied from a broad statistical viewpoint and should be correlated with the incidence of disease.

In a recent statistical study[2] the author has attempted to correlate some of these factors with the incidence of heart disease on a broad countrywide and worldwide basis. The marked variability in the incidence of arteriosclerotic and hypertensive heart diseases in various parts of the country and the world over was found to have some relationship to the ethnic origin of peoples, geographic location, predominance of urban versus rural inhabitation and seasonal variation. These and many other factors call for more thorough study.

That multiple factors enter into the etiology of heart disease is well illustrated by the development of rheumatic heart disease. Whereas it has been well established that this form of heart disease follows streptococcal infections or scarlet fever, it has been shown statistically that only about 3% of cases with such infection will develop rheumatic fever. Evidently there must be additional factors besides the effect of streptococcal infection which are operative in the causation of this disease. We may, of course, argue that immunity may be the protective factor, but why should only relatively few people not have such immunity? Why should there be a greater tendency for the disease to develop under poor environmental conditions? Why is it more frequent in certain families? Why is it more frequent in certain seasons of the year?

Further clinical observations and broader statistical studies should help solve many of the etiologic factors concerned with the causation of heart disease.

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Clinical Studies

Use of Radioactive Iodine in the Treatment of Angina Pectoris*

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THE CONCEPT of the treatment of intractable angina pectoris by the deliberate induction of a myxedematous or hypothyroid state was first proposed in 1933 by Blumgart, Levine and Berlin.[1] The treatment is symptomatic and does not affect the underlying disease process. The basic pathology remains. The improvement in cardiac symptomatology is, at least in part, due to the physiologic changes accompanying a lowered metabolic level, which result in lowered demands on the heart and coronary circulation.[1,2]

Treatment is restricted to that small percentage of patients with angina pectoris who develop incapacitating anginal pain, not relieved by all the usual therapeutic measures properly applied. Even in a large clinic such patients are relatively infrequent.[3]

HISTORICAL

Although this concept of the palliative treatment of intractable heart disease by ablation of the thyroid gland and subsequent lowering of the metabolic rate is relatively recent, its roots are old. Parry, in his original description of exophthalmic goiter in 1825, noted an interrelationship between cardiac symptomatology and goiter.[4] Later workers, notably Kocher and Bilroth, observed that angina pectoris and congestive heart failure, often present in their thyrotoxic patients, were benefited by thyroidectomy.[3] Lahey and his associates, after considerable experience with thyrocardiacs, noted that even patients with severe angina or failure did well following thyroidectomy.[5]

However, it was not until 1933 that Blumgart, Levine and Berlin published a preliminary report on the results of induced hypothyroidism.[1,2] As Blumgart later stated,[3] "the induction of hypometabolism to alleviate intractable heart disease in patients with normal thyroid function is a natural extension of the favorable cardiovascular effects of lowering the high metabolic rate of thyrocardiac patients to normal" .... "if the normal metabolic rate of the patient with congestive heart failure or angina pectoris was reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of the body."[1]

The changes in cardiovascular function in myxedema may be summarized briefly as follows:

In myxedema there is a reduction in the basal metabolism, i.e., a diminution in the oxygen consumption in the tissues. The circulatory changes may be viewed as compensatory mechanisms of the body adjusting to the reduced oxygen need of the tissues and to the lowered heat production of the body. The reductions in the peripheral blood flow, venous return, blood volume, work of the heart, and cardiac output all comprise these readjustments. The fall in cardiac output is due to both the diminished heart rate and reduced stroke vol-

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ume. The slowing of the peripheral bloodstream permits greater oxygen utilization by the tissues; hence there is an increased arteriovenous oxygen difference.[6,7]

Surgical Thyroidectomy: Following the original report of Blumgart *et al.* many clinics attempted total surgical thyroidectomy in patients with intractable congestive heart failure and intractable angina pectoris. There was a great variation in results by different investigators. However, on analyzing the results of those who were most vehement in their criticisms of the procedure, it is noteworthy that the results in the cases with intractable congestive failure were poor, while the improvement in those with angina was considerably better.

In 1937, Parson and Purks reviewed the literature and surveyed the major clinical centers as to their results using surgical removal of the thyroid to induce hypometabolism in cases of intractable angina pectoris and congestive heart failure.[9] Total thyroidectomies had been performed on 133 patients with angina pectoris. There was an operative mortality of 3.5 per cent. Of the survivors, 71 patients or 55.5 per cent showed excellent results, 36 patients or 28 per cent showed moderately good results, 5 patients or 4 per cent showed only minimal or slight improvement and 16 or 12.5 per cent showed no improvement. The number of complications, however, was significant: 8.2 per cent of the patients had hoarseness due to laryngeal nerve injury and 10 per cent had tetany. These changes were transient in all but one instance of each complication.

Because of the operative mortality and the complications attendant upon this form of therapy, it gradually lost popularity.

Thiourea Derivatives: With the introduction of the thiourea derivatives, however, there was a revival of interest in the treatment of patients with intractable angina pectoris by the induction of hypometabolism. The thiourea derivatives act by blocking the enzymatic "organification" of iodide within the thyroid gland. This prevents the formation of thyroid hormone with resultant lowering of the amount of circulating hormone and finally produces hypometabolism. However, the enzymatic block is not complete and it is difficult to produce complete myxedema. In addition, the incidence of agranulocytosis, while small, constitutes a definite hazard and necessitates blood counts as long as the medication is used. Drug fever, rashes, alopecia, etc. have also been reported with these drugs, although infrequently. Finally, the drug must be continued throughout the patient's lifetime, since the block lasts only as long as the use of the drug is maintained.[3,10]

Radioactive Iodine: The advent of radioactive iodine made available a method for the nonsurgical induction of permanent hypometabolism by irradiation of the thyroid gland. The metabolism of iodine is such that the radioactive isotopes of iodine offer a very effective method for localizing the radioactivity to the thyroid gland with relatively small amounts of generalized body irradiation. The pioneer work in this field was reported by Blumgart and his associates.[3]

Radioactive iodine is commonly used as sodium iodide 131. This isotope of iodine has a half-life of eight days and decays by the emission of beta and gamma radiation. Most of the radiation dose is due to beta radiation of I^{131} which has a maximum range of approximately 2 mm in tissues so that radiation of the parathyroid and perithyroidal tissues is insignificant.[3,11]

Selection of Patients

The indications for treatment can be divided into two main groups: those concerned with severity of the anginal syndrome and those concerned with the stability of the process. We have treated patients only when we were convinced that the anginal syndrome was incapacitating and refractory to standard therapeutic measures. Decubitus angina was accepted as prima facie evidence of incapacity. Inability to fulfill the normal requirements of sedentary life without disabling pain was also accepted. We have insisted in so far as practical on the exclusion of noncardiac causes of the anginal syndrome. Electrocardiographic evidence of a previous myocardial infarct has not been required prior to treatment. In general, these criteria of severity have been accepted by all groups using this form of therapy.[12,14–20]

Angina pectoris waxes and wanes both in frequency and severity in treated and untreated

patients. The stability of the anginal syndrome is therefore to be taken into consideration. Some clinics have insisted that the anginal syndrome be stable for periods of time varying from three months to one year prior to treatment. We have usually required at least two months of incapacitating pain before accepting a patient for treatment.

Other investigators have considered as relative contraindications to treatment, several diseases that might be adversely affected by the induction of myxedema. They can be divided into (1) diseases of metabolism, i.e., hypercholesterolemia and diabetes, (2) peripheral vascular disease, (3) other disease states including arthritis, and (4) severe anxiety states. In addition, some groups have assumed that the use of tobacco is a contraindication to treatment. We have considered only two contraindications to therapy: (1) the presence of a recent myocardial infarct, or (2) pre-existing myxedema.

Procedure

The patients were given a tracer dose of radioactive iodine and the uptake by the thyroid gland was measured at 24 hours by the usual method. In each patient, hyperthyroidism was excluded not only by a clinical evaluation but also by means of the uptake and where necessary by blood turnover studies (PBI^{131}) and the PBI^{127} of the serum. In our laboratory, most euthyroid patients have an uptake of less than 55 per cent at 24 hours. The patients were then given a therapeutic dose of radioactive iodine. The normal thyroid is relatively resistant to radiation. In most patients between 30,000 and 50,000 rads are necessary to cause ablation of the thyroid gland. The amount of radioactive iodine necessary to deliver this amount of radiation to the thyroid gland depends upon the size of the gland, the administered dose, the uptake by the thyroid gland, and the effective half-life of the retained I^{131}.

After 8 to 12 weeks the clinical results were evaluated. The degree of clinical improvement, if any, was noted and the presence or absence of hypothyroidism determined. A second radioactive iodine uptake (with due allowance for residual background of radioactivity present in the thyroid gland following the first therapeutic dose) was determined at this time. If adequate clinical response had occurred or complete myxedema was present, no further therapy with radioactive iodine was carried out. If there was an unsatisfactory clinical response and myxedema was not present, a second therapeutic dose was administered. A similar routine was followed at three-month intervals until either a clinical response had occurred or myxedema was present and had been confirmed by appropriate laboratory studies. (The use of thyroid extract when the symptoms of hypothyroidism became disturbing to the patient is discussed in a later paragraph).

In some patients who became myxedematous there was later regeneration of the remaining portions of thyroid and return of thyroid function to a euthyroid state. These patients usually had nodular goiters and it is presumed that some of the resting areas not destroyed by the initial I^{131} radiation resumed normal function. Such patients may require retreatment.

Results

It is difficult to evaluate the results of this form of palliative therapy objectively because of the following factors: first, the severity of symptoms is based solely on subjective data; second, the symptoms of angina pectoris exhibit spontaneous remissions and exacerbations; and, finally, patients with angina pectoris have at times shown a dramatic response to various forms of placebo therapy. In radiation thyroidectomy we have however, a built-in safeguard to exclude a "false" response to therapy. In the induction of a hypothyroid state there is a lag period of about three weeks following the use of radioactive iodine during which no clinical improvement is to be expected. Improvement in any patient noted during this period is either due to spontaneous improvement or, more likely, to psychologic effects of therapy and is not a true therapeutic response. (None of our patients was told prior to therapy when clinical improvement could be expected.)

Taking into consideration some objective guides which have been proposed, such as the degree of exertion required to produce angina and the amount of nitroglycerine necessary to

control the pain, we have classified the results as follows:

Excellent: Patient was essentially free of angina and able to assume a reasonably normal life.

Good: There was a significant reduction in the frequency and severity of the anginal attacks. Angina decubitus, if present prior to therapy, was completely relieved.

Fair: Some lessening of the frequency and severity of attacks occurred, but definite impairment of activity was still present.

Poor: Severity and frequency of attacks were unchanged (or worse).

Various groups have used essentially similar criteria in evaluating their results. Some have combined the excellent and good results into a single group.[12–20]

Our series consisted of 65 patients who have been treated by us over the past 8 years. These patients have been followed for a period of at least 6 months following the induction of a hypothyroid or myxedematous state. They are private patients or clinic patients selected from the wards and clinics of The Mount Sinai Hospital. There were 46 males, ranging in age from 34 to 72, and 19 females, ranging in age from 46 to 74. The results reported by others and by us are tabulated in Table I. It should be remembered that these results were obtained in patients who had been uncontrolled by conventional therapy.

Seven of our patients were followed between 6 months and one year following the induction of hypothyroidism; 27 for one to two years; 17 for two to five years; and two for more than five years. One year following therapy one patient died of a myocardial infarction, another died two years following therapy of a cerebral hemorrhage, a third died 18 months after treatment with congestive heart failure following another myocardial infarction. A fourth died three years after therapy of metastatic carcinoma primary site probably intestinal. There were 8 deaths which occurred within three months after therapy. These are discussed later in the paper.

Case Histories

The following case histories are perhaps more indicative of the value and results of this therapy than the statistics noted above. One example of each class of results is given:

EXCELLENT RESPONSE

Case 1. This patient was a 67-year-old male who had arteriosclerotic cardiovascular disease. In 1952 he had a proven myocardial infarct and since that time he has had decubitus angina and has been in cardiac failure. He received the usual therapy for congestive heart failure including mercurial diuretics; Demerol® was at times necessary to control the angina pectoris. For one year prior to treatment, the patient had received 500 mg of propylthiouracil daily with a poor response. For approximately six months prior to treatment, the patient had required a nurse at home to give him

TABLE I

Summary of Therapeutic Results in the Treatment of Angina Pectoris by I^{131}

	Authors' series		Jaffe[18]		Blumgart[12]		Wolferth[17]		Chapman[19]		Goldman[20]		Blumgart[12] (combined from 50 clinics)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Excellent	15	23	53	56	24	39	12	67	4	44	5	38	284	39
Good	23	35	35	37	20	32	4	22			3	24	257	36
Fair and poor	19	30	6	7	18	28	2	11	5	56			179	25
Died	8	12*	16†								5	38		
Total	65		110		62		18		9		13		720	

* Three other deaths are included in the excellent, good, fair and poor categories.

† Jaffe included seven of these deaths in his excellent category, seven in the good, and two in fair and poor.

demerol and oxygen during the night because of the frequent attacks of decubitus angina. Obviously, he had been unable to work.

Physical Examination: The patient was acutely ill, thin, and sallow. Pertinent physical findings were as follows: Weight 124 lb, blood pressure 130/80, pulse 96. The heart sounds were distant. A_2 was greater than P_2. There was enlargement of the heart to the left. The point of maximal impulse was in the 6th intercostal space just lateral to the midclavicular line. The thyroid gland was not felt and the thyroid status, clinically, was normal. There was no arthritis and minimal anxiety. Peripheral pulses were just palpable. Liver was palpable one finger below the right costal margin. Radioactive iodine uptake was 75 per cent at 24 hours. Blood turnover studies (PBI^{131}) were within normal limits (0.08 per cent of the administered dose per liter of plasma at 72 hours). The high uptake value is due to a rebound effect following propylthiouracil therapy.

Course: The patient was treated with 25 mc of I^{131} on May 1, 1954. On July 2, 1954, the patient reported that he had been able to walk approximately twelve blocks and on that day he received an additional 20 mc. For the past two years the patient has worked as an executive. There is no longer any need for oxygen. He has had only occasional attacks of angina during the day. He receives an injection of mercurial diuretic once every two weeks. No further therapy has been given. He has clinical myxedema confirmed by an I^{131} uptake value of 5 per cent at 24 hours in September 1954.

GOOD RESPONSE

CASE 2. A 72-year-old white male had had a coronary artery occlusion in 1941. Following this he had had typical anginal pain including radiation down the left arm which had been refractory to the usual forms of therapy. For two years prior to treatment, he had noted intermittent pain in both legs after walking two blocks. This second factor probably kept the number of anginal attacks per day to a minimum. The patient had never been in congestive heart failure. He was, however, diabetic and was controlled by diet alone without the use of insulin. The remainder of the functional inquiry and past history were noncontributory. Clinically, he was euthyroid.

The patient occasionally required as many as 14 to 16 nitroglycerine tablets per day and averaged somewhere between six and ten per day.

Physical Examination: The patient was a well-developed, fairly well-nourished white male, 72 years of age. Blood pressure was 200/80, pulse 96 and regular. Positive physical findings were confined to the heart. A_2 was ringing, much louder than P_2. No diastolic murmurs were heard. The heart was enlarged to the left, the point of maximal impulse being noted one inch lateral to the 5th intercostal space in the midclavicular line. The thyroid was not palpable.

Course: On February 24, 1954, radioactive iodine uptake by the thyroid gland was 43 per cent. The patient received a therapeutic dose of 10 mc of radioactive iodine. Two months later, his uptake had fallen to 28 per cent. His angina was slightly improved. At that time, he received 23 mc of radioactive iodine. His uptake two months later was 21 per cent. He again received 23 mc of radioactive iodine. Five months after initial treatment the patient had no angina. Blood pressure was 190/90; he had myxedema and because of his symptoms he was maintained on thyroid extract, $^1/_2$ grain per day. The patient used only two nitroglycerine tablets in approximately ten days. He had cramps in his leg on stretching, but this was not a disturbing symptom. The total period of follow-up was two years. The improvement has continued with no further therapy.

FAIR RESPONSE

CASE 3. This 65-year-old female had had a coronary artery occlusion in 1945 and a second myocardial infarction in 1954. For one year the patient had had frequent episodes of typical anginal pain. She had used between 10 and 15 nitroglycerine tablets per day. The pain had failed to respond to the usual forms of therapy. She was tense and anxious. The remainder of the history was not contributory. Thyroid status prior to treatment was normal.

Physical Examination and Course: The patient was a well nourished, well developed, slightly obese, white female in no distress. Blood pressure was 150/90, pulse 88 and regular.

On June 2, 1953, the radioactive iodine uptake by the thyroid gland was 46 per cent. She received 15 mc of radioactive iodine as a therapeutic dose. Two months later, there was no improvement. She received an additional 20 mc of radioactive iodine. She was maintained on thyroid, $^1/_2$ grain every day. Attacks were decreased in frequency and severity. Clinical myxedema was present.

POOR RESPONSE

CASE 4. A 65-year-old woman who had arteriosclerotic cardiovascular disease had used about 40 nitroglycerine tablets daily for typical anginal attacks.

Physical Examination: The heart was minimally enlarged. A_2 was ringing. There were no other significant findings. The thyroid gland was not felt. Blood pressure was 140/100. Weight 118 lb.

Course: Uptake of radioactive iodine prior to examination was 38 per cent. She received 25 mc of radioactive iodine on September 11, 1953, and two months later 20 mc of I^{131} as therapeutic doses.

She developed myxedema without any relief of her anginal pain. To control the symptoms of myxedema, she was finally placed on one grain of thyroid extract daily. The final evaluation was made two and one-half years after therapy.

TABLE II

Effect of Associated Cardiac Manifestations on Therapeutic Results Following the Use of I^{131} for Angina (Authors' Series)

Entire series		Number of patients		Results									
				Excellent		Good*		Fair†		Poor		Died‡	
		65	%	15	%	23	%	9	%	10	%	8	%
Angina decubitus	Present	28	43	10	67	8	35	3	33	5	50	7	87
	Absent	37	57	5	33	13	65	6	67	5	50	1	13
Known myocardial infarct	Present	20	31	5	33	7	30	3	33	2	20	4	50
	Absent	45	69	10	67	16	70	6	70	8	80	4	50
Tachycardia, pulse over 90	Present	15	23	2	13	4	17	2	22	3	30	4	50
	Absent	40	77	13	87	19	83	7	78	7	70	4	50
Hypertension	Present	20	31	4	27	6	26	3	33	4	40	3	37
	Absent	45	69	11	73	17	74	6	67	6	60	5	63
Congestive heart failure	Present	9	14	1	7	4	17	1	11	2	20	1	13
	Absent	56	86	14	93	19	83	8	89	8	80	7	87

* Two patients, both of whom had good results had had a previous cardiopexy for anginal pain without relief.
† One patient died of cerebral hemorrhage two years after therapy.
‡ Within three months after therapy.

Evaluation of Results

Influence of Various Cardiac Factors: Table II presents an analysis of the influence on the final result of the following cardiac findings: (a) decubitus angina, (b) previous known myocardial infarct, (c) tachycardia, (d) hypertension, (e) congestive heart failure. None of these factors had any influence on the therapeutic results with the exception of decubitus angina. The eight deaths occurred in patients who had had decubitus angina. However, this form of angina always carries the poorest prognosis. The natural history of angina pectoris is such that it is extremely difficult to decide in any given patient whether the sudden death is part of the course of the disease or the result of the therapy; there may also be a combined effect. It may also be noted that a high proportion of excellent results occurred in these patients.

Two patients who had persistent severe angina pectoris following a pericardiopexy had good results following I^{131} therapy.

Effect on Associated Diseases: The presence of certain metabolic diseases, including cirrhosis, arthritis,[1] diabetes mellitus, hypercholesterolemia and claudication, is considered a contraindication to this form of therapy by some groups. We therefore examined both the effects of our therapy on angina pectoris in the presence of these concomitant diseases and the changes, if any, induced by therapy in these diseases themselves.

Of the four patients with diabetes mellitus, one had an excellent response, two had a good response, and one died. No adverse effects on the diabetes mellitus were noted; in some the insulin requirement was reduced. Of the six patients with arthritis (hypertrophic osteoarthritis), three had excellent results with no increase in the symptoms of arthritis, three had a fair response with some increase in the symptoms of arthritis. In the seven patients with claudication, there was no increase in muscle cramps or leg pains. One of these had an excellent response, three a good response, two a poor response and one died. Of our three patients with hypercholesterolemia, one had an excellent response, two a good response. None of our patients had cirrhosis.

Five patients had been treated for hyper-

TABLE III

Average Administered and Retained Dosage of I^{131} According to Results Obtained (Authors' Series)

	Excellent (15 cases)		Good (23 cases)		Fair (9 cases)		Poor (10 cases)		Died (8 cases)	
	Administered dose in mc of I^{131}	Retained dose	Administered dose in mc of I^{131}	Retained dose	Administered dose in mc of I^{131}	Retained dose	Administered dose in mc of I^{131}	Retained dose	Administered dose in mc of I^{131}	Retained dose
Maximum	45	22	140	45	40	18	80	22	40	27
Minimum	15	8	15	7	30	7.5	42	6	12	6
Average	24	12.5	34.2	9.0	33.0	13.0	32.0	10.1	26.3	12.2

NOTE: In some of these cases retained dose could not be determined because uptake percentage was not determined for each administered dose. All figures refer to millicuries of I^{131}.

thyroidism earlier and were euthyroid at the time of therapy for angina pectoris (two had had subtotal thyroidectomy for hyperthyroidism and three had been treated with radioactive iodine). Of these patients, three had an excellent response to therapy and two had a fair response. It is our feeling that once a patient with hyperthyroidism has been returned to a euthyroid level, he should be regarded as any other euthyroid cardiac.

There is no evidence in our series that sex, age or economic status (private or ward) had any influence upon the results obtained.

Analysis of Therapeutic Failures

One of the reasons for failure of this type of treatment would be failure to induce hypothyroidism. As long as sufficient irradiation to produce myxedema is given, the actual size of either the administered dose or of that retained by the thyroid appears to have little bearing on the final results (Table III).

We reviewed the 19 cases in which a fair or poor response had been obtained to determine if sufficient therapy had been given. Only two patients did not have myxedema, and no reason for withholding additional treatment from these patients is known. Six patients, subsequent to the initial course of therapy, suffered another myocardial infarct and were not retreated. Of the remaining 11 patients in this group, no special reason for failure was observed; all had myxedema.

Adverse Effects

In any form of therapy there may be side-effects which are undesirable and disturbing to the patients. This is particularly true of palliative therapy such as this, which induces a second and new disease state. In the final evaluation, these undesirable side-effects must be weighed against the symptomatic relief of pain that is obtained.

Myxedema: The generalized side-effects are primarily those due to the induction of myxedema. Sluggish mental functioning and muscle cramps were the two most common complaints. Some patients also noted cold skin, tendency to fatigue, and general lassitude.

The therapeutic goal of this treatment is the relief of the cardiac symptomatology; it is not the production of myxedema. Some patients do well from a cardiac point of view when they are maintained in a hypothyroid state whereas others require clinical myxedema for relief. We have therefore attempted to control these undesirable symptoms of myxedema by the use of small doses of thyroid extract. The sensitivity of patients with myxedema or hypothyroidism to thyroid extract is well known. Doses as small as 30 mg to 60 mg of thyroid extract daily would occasionally cause a complete recurrence of the anginal syndrome. Slightly less than half of our

patients were maintained on doses of thyroid ranging from 6 to 50 mg of thyroid extract per day. By adjusting the daily dose of thyroid extract, we attempted to keep these patients free of their anginal attacks and at the same time to alleviate the most disturbing symptoms of myxedema.

Toxic Effects of Radiation: In addition to the myxedema there are the inevitable side-effects of general body irradiation. For every millicurie of I^{131} administered there is a total body dosage of approximately 1 rad. The carcinogenic and leukemogenic effects of radiation have received wide publicity recently, but at the present time there is no evidence that I^{131} in the doses required for therapy is carcinogenic or leukemogenic. Mild parotitis due to irradiation of the salivary glands may be noted during the first three days of therapy.

Radiation Thyroiditis: Finally, there are the effects of radiation on the thyroid gland itself. A reaction known as acute radiation thyroiditis may occur when high doses of radiation are delivered to the thyroid gland over a short period of time. This reaction is characterized clinically by pain and tenderness over the gland and a mild febrile response. It usually occurs between the third and tenth day following the initial treatment. There is necrosis with breakdown of the structure of the gland and release of preformed thyroid hormone into the circulation. If a large amount of thyroid hormone is released into the bloodstream, an acute, but transient, hyperthyroidism ensues with an elevation of the pulse rate, widening of the pulse pressure, increase in the basal metabolic rate, increase in the work of the heart and cardiac output. Since these alterations are obviously the antithesis of those intended by this therapy, they may have serious consequences in patients who have maintained a marginal cardiac existence. In some, these demands may prove overwhelming for a damaged heart.

The following case history is illustrative of this reaction.

Case 5. This white male first developed typical angina pectoris in 1948 at the age of 57. In June, 1954 he suffered an attack of acute coronary artery thrombosis of moderate severity. For three months after the attack his anginal seizures seemed less severe but then recurred with their former severity and frequency. When seen by us in November, 1955, he was suffering from intractable angina pectoris and had been compelled to give up practically all activity. He used as many as 20 tablets of nitroglycerine daily and frequently required narcotics for relief. He had recurrent decubitus angina and could not walk two blocks without pain, even at a very slow pace. There were no evidences of congestive heart failure. The blood pressure was 144/80 and the pulse rate was 82 per min and regular. The heart was slightly enlarged to the left. He was considered a suitable case for I^{131} therapy.

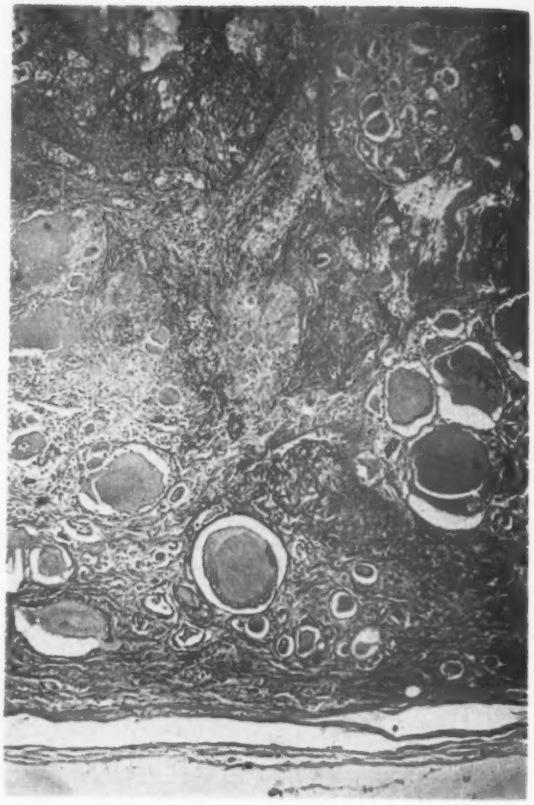

Fig. 1. Microscopic section of thyroid gland 25 days after I^{131}. Severe acute radiation thyroiditis.

Clinical Course: On November 15, 1955 a tracer study with I^{131} revealed an uptake of 44 per cent of the tracer dose in the thyroid gland at the end of twenty-four hours. On November 16, 1955 a therapeutic dose of 35 mc of I^{131} was administered orally. Assuming a thyroid weight of 30 g and an effective half-life of six days this dose would deliver about 48,000 rads to the thyroid gland over the period of its decay. This rather high dosage was given with the hope that complete thyroid ablation could be accomplished with one dose. On the fifth day after treatment the thyroid gland became tender and painful and there was some radiation of the pain to the angles of the jaws and behind the ears. By the sixteenth day after treatment it was apparent that

TABLE IV

Data on Patients Who Died Within Three Months of First Treatment With I^{131}

	Sex	Age	Duration of intractable angina	Angina decubitus	Dose administered mc I^{131}	Dose retained by thyroid mc I^{131}	Radiation thyroiditis	Time post-treatment	Related to treatment
1.	M	71	6 mo	Yes	28	9	No	3 wk	No? CHF
2.	M	64	2 yr	Yes	35	16	Yes	3 wk	Yes
3.	M	61	7 yr	Yes	30	16	Yes	1 mo	Yes
4.	M	59	11 yr	Yes	40	27	Yes	3 wk	Yes
*5.	M	68	2 yr	Yes	12	6	?Yes	4 wk	?
*6.	M	52	6 mo	Yes	15	7.5	Yes	2 mo	No
7.	M	64	15 yr	Yes	32	15	No	3 mo	No
*8.	M	51	7 yr	Yes	15	7	Yes	3 mo	No

* These patients at the time of treatment were thought to have an impending coronary occlusion because of the recent exacerbation of symptoms.

the patient's condition was deteriorating. His angina was increasing in severity and frequency and symptoms of an induced hyperthyroid state were present. These included tachycardia, sweating, a PBI elevation to 10.3 mg per 100 ml of plasma and electrocardiographic evidences of coronary insufficiency not previously present, as well as evidences of the previous myocardial infarction. He was hospitalized but in spite of active therapy the patient died on the ninth hospital day, 25 days after the administration of the therapeutic dose of I^{131}.

Postmortem Examination: This revealed evidence of arteriosclerotic cardiovascular disease with an old occlusion of the left anterior descending coronary artery. There was a fresh thrombosis in the mid-portion of the right coronary artery.

Thyroid Gland: The gland was smaller than normal and, except for an outer rim, showed evidence of acute necrosis with hemorrhage. On microscopic examination the gland showed evidence of diffuse necrosis and loss of staining characteristics (Fig. 1). Cell structure was indistinct and there was some infiltration with leukocytes. Cell structure was fairly well maintained at the periphery of the gland, probably due to the smaller dose of radiation received in this area.

Comment: This 64-year-old man with a known previous myocardial infarction had severe intractable angina pectoris without congestive failure. He received a therapeutic dose of 35 mc of I^{131} (15.4 mc retained in the thyroid gland). He developed an acute radiation thyroiditis with pain and tenderness over the gland and, secondary to the release of preformed thyroid hormone, tachycardia and a mild febrile response. His cardiac status deteriorated. His angina pectoris increased in severity and frequency. He developed severe chest pain. He was admitted to the hospital in failure and expired despite all therapeutic measures three weeks after therapy. An elevated protein-bound iodine showed that there was release of preformed thyroid hormone. At postmortem examination a recent myocardial infarction was found. Radiation thyroiditis was noted on examination of the thyroid gland. The question of whether the thyroiditis and the induced hyperthyroid state caused overwhelming demands on this previously damaged heart and thus precipitated the patient's death cannot be answered with certainty.

Review of Fatal Cases: Following this experience, we analyzed the deaths that had occurred in this series within three months of treatment. The results are presented in Table IV. Because of the unpredictable course of angina pectoris, it is difficult to decide whether death is due to therapy, the underlying disease or a combination of both. On a clinical basis, deaths occurring within the first month following treatment could conceivably be related to therapeutically induced radiation thyroiditis and the resultant hyperthyroidism. It should be noted that in three of the five deaths that occurred within one month of therapy there was an exacerbation of cardiac symptoms possibly secondary to an acute radiation thyroiditis.

The severity of this reaction is proportional to the amount of thyroid hormone released. The amount of hormone released is dependent upon (1) the amount of necrosis produced at one time and (2) the amount of stored hormone. We can, within limits, regulate the amount of acute necrosis produced by altering our time-

dose relationship. By fractionating the dose of I^{131} necessary to cause ablation of thyroid function over a period of time, we can prevent acute necrosis of the thyroid gland and the subsequent release of large amounts of preformed thyroid hormone into the circulation.

Prevention of Adverse Radiation Effects: One fact emerges from this review of the deaths in our series. The reaction of severe acute radiation thyroiditis occurred only in those patients who received a retained dose of more than 12 mc as the initial dose. Our present schedule is to give the first series of treatments in two or three fractional doses at weekly intervals. In 20 patients on this regimen we have not seen any significant aggravation of symptoms. The first dose should be selected so that not more than 7 mc are retained by the normal-sized thyroid gland.

Another method of preventing the undesirable effects of the sudden release of excessive thyroid hormone into the circulation is pre-treatment of the patients with antithyroid drugs. These drugs deplete the gland of stored hormone and larger doses of radiation can then be delivered safely to the thyroid gland without danger although the necrosis may be extreme.

Conclusions

(1) In intractable angina pectoris, the induction of myxedema or a hypothyroid state by ablation of the thyroid gland with I^{131} is of definite value for producing symptomatic relief. Approximately 25 per cent of the patients had an excellent response, 35 per cent had a good response, and 40 per cent had a fair or poor response.

(2) The indication for treatment is severe intractable angina pectoris of relative stability which has been resistant to standard cardiac therapy.

(3) The contraindications for therapy (we have used) are pre-existing hypothyroidism and recent coronary artery occlusion.

(4) The undesirable side-effects are primarily those secondary to myxedema and to generalized body irradiation.

(5) Symptoms of myxedema can be partially controlled by the administration of small doses of thyroid extract, without reactivating the angina.

(6) Acute radiation thyroiditis may cause transient hyperthyroidism and this may be a contributory cause of death following therapy. Adjustment of time-dose relationship may prevent this reaction. A maximum initial dose of 7 mc retained in the gland of normal size is suggested.

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Acute Myocardial Infarction in a City Hospital*

I. Clinical Review of 264 Cases

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THIS IS a report of clinical observations on 264 cases of acute myocardial infarction at Kings County Hospital during a one-year period. A city hospital population is composed of a somewhat different group of patients than private or voluntary institutions, with resultant differences in clinical course and survival. Widespread hospitalization insurance, socio-economic status and hospital admission policy are, in part, significant determinate factors. City hospital patients are usually more critically ill and experience a greater delay in time before hospital admission, and as a result thereof, have a decreased chance of survival. The results of anticoagulant therapy, the experiences with the therapy of shock accompanying myocardial infarction, and a clinico-pathological correlation will be reported in subsequent publications.[1,2,3]

MATERIAL

The records of all patients discharged from the University Medical Division II of the Kings County Hospital with a diagnosis of acute myocardial infarction (standard nomenclature number 430–516.7) between July 1, 1954, and June 30, 1955, were examined. There were 394 cases of which 264 satisfied at least one of the following criteria: (1) demonstration at autopsy of an acute myocardial infarct, (2) electrocardiographic demonstration (usually in a 12-lead tracing) of serial changes compatible with acute myocardial infarction, or (3) a history suggestive of acute myocardial infarction without diagnostic or any electrocardiographic changes in patients with a previous history of coronary artery disease followed by temperature over 100° rectally or by leukocytosis over 10,000 or by elevation of erythrocyte sedimentation rate, not explainable by any other recognized disease.

TABLE I

Category of Cases Reviewed

I.	Cases signed out as acute myocardial infarction	394
II.	Cases satisfying criteria for acute myocardial infarction	264
III.	Cases not satisfying criteria for acute myocardial infarction	130
	(a) Insufficient evidence of acute myocardial infarction	66
	(b) No evidence of acute myocardial infarction	64
	(1) Old infarction	18
	(2) Angina pectoris, "coronary failure," or other diseases	46

Table I categorizes the 130 cases which did not satisfy the above criteria. Those 66 cases which are listed under the heading of "insufficient evidence" were probably additional cases of acute myocardial infarction and included: (1) deaths within a few hours of hospital admission without benefit of one or all of the following: (a) adequate previous history, (b) laboratory studies, (c) electrocardiogram, or

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(d) autopsy; (2) surviving patients with an equivocal clinical story in the absence of electrocardiographic changes or without available electrocardiograms, in the presence of other disease. It is understood that by the exclusion of these 66 records some acute myocardial infarctions resulting in sudden death are probably being omitted, and also that certain surviving patients without changes in electrocardiogram have been also omitted from the study. It is intended, however, to include only those cases with unequivocal evidence of acute infarction, and it appears unlikely that a significant number of cases have actually been excluded. In a recent report[4] of 100 autopsied cases of acute myocardial infarction, diagnostic or suggestive evidence of this lesion was present in 86 per cent of 85 electrocardiograms. In another report[5] only one of 50 patients with classic clinical evidence of myocardial infraction revealed no significant changes in 12 electrocardiographic leads. According to Wolff,[6] electrocardiograms are either diagnostic or show nondiagnostic abnormalities in all cases of acute myocardial infarction with the exception of infarcts which are very small, entirely intramural, situated away from the leads obtained, or in the presence of left bundle branch block.

Those cases labeled "no evidence" were considered to be compatible with diagnoses of angina pectoris, "coronary failure,"[7] pneumonia, bronchogenic carcinoma, cholecystopathy, or other diseases. In many such cases there was no laboratory evidence compatible with acute myocardial infarction, and electrocardiograms were compatible with the old myocardial infarction.

Results of Study

GENERAL DATA

The *ages* of the patients varied from 32 to 97 years with an average of 68 years and a median of 64½ years. Table II lists all the ages of the cases by one-half decades. Classified according to *race*, there were 260 White, three Negro and one Yellow. Of the three Negroes, two were male and one was female; the Yellow patient was male. The over-all hospital population during the study period was 74.5 per cent White, 25 per cent Negro, and 0.5 per cent other. *Males* constituted 162 cases (61 per cent) and females 102 (39 per cent). There were 45 per cent males in the general hospital census during the same year. *Religion* was recorded in 171 records, of which there were 108 Hebrew (63 per cent), 50 Catholic (29.5 per cent), and 13 Protestant (7.5 per cent). There were 14 per cent Hebrew, 24 per cent Catholic and 45 per cent Protestant patients in the hospital at that time. The habit of *smoking* was stated in only 96 cases, of which 56 patients affirmed and 40 patients denied smoking. Insufficient total data preclude further discussion of the relationship of smoking and myocardial infarction.

TABLE II
Age Distribution of Patients

Age	Number of patients	Age	Number of patients
31–35	1	66– 70	48
36–40	3	71– 75	52
41–45	2	76– 80	25
46–50	17	81– 85	16
51–55	21	86– 90	1
56–60	33	91– 95	0
61–65	43	96–100	2
Total	120	Total	144

FAMILIAL HISTORY

Among the familial histories of cardiovascular disease and diabetes there were 20 instances

TABLE III
Patients with a History of Previous Angina Pectoris

Duration	Number of patients
1–7 days	18
1–4 wk	19
1–3 mo	12
3–12 mo	8
1–2 yr	16
2–5 yr	35
5–10 yr	17
10+ yr	7
Total	132
Unspecified	36
No angina	96

of a definite history of myocardial infarction, 21 of unclassified heart disease, 18 of hypertension, 10 of cerebrovascular accident, and 19 of a familial history of diabetes mellitus. The overall incidence of cardiovascular disease including diabetes mellitus was 49 per cent, or 38 per cent excluding diabetes.

PAST MEDICAL HISTORY

A history of antecedent *angina pectoris* was obtained from 148 of 244 patients (61 per cent), concerning whom a definite history was available. Table III provides the time interval between the onset of angina pectoris and the acute myocardial infarct. Of the 96 patients who were classified as having had no angina, a questionable or equivocal history was available in 12. There were 23 persons with a combined history of previous angina pectoris and myocardial infarction. The occurrence of angina pectoris of more than ten years' duration in seven patients is noteworthy. A history of previous *myocardial infarction* was recorded in 61 instances (23 per cent) with three previous episodes of infarction in each of two patients and two prior infarcts in each of four patients (see Table IV). An antecedent history of *congestive heart failure* was obtained from 113 of 255 records (44.3 per cent). (Table V.) Congestive heart failure was diagnosed on the basis of a history of exertional dyspnea or orthopnea in the absence of primary pulmonary or of other predisposing disease.

Hypertension, by history, existed in 86 of 232 cases (37 per cent), but the data are considered unreliable, inasmuch as actual blood pressure readings were seldom available prior to hospitalization. (Table VI.) There were 22 records of previous *cerebrovascular accidents*, two of which were noted within one week of the acute myocardial infarct. (Table VII.) There

TABLE IV

Patients with Evidence of a Previous Myocardial Infarct

Interval before present attack	Number of patients
1–2 mo	4
2–3 mo	7
6–12 mo	6
1–2 yr	8
2–5 yr	17
6–10 yr	8
10+ yr	7
Unspecified	4
Total	61

TABLE V

Previous Congestive Failure

Duration	Number of patients
Less than 1 mo	8
2–5 mo	9
6–12 mo	7
1–5 yr	36
6–10 yr	13
10+ yr	3
Unspecified	37
Total	113

TABLE VI

Patients with a History of Previous Hypertension

Duration	Number of patients
Less than 1 yr	3
1–5 yr	34
6–10 yr	15
10+ yr	11
Unspecified	23
Total	86

TABLE VII

Patients with a History of Previous Cerebrovascular Accident

Duration	Number of Patients
2 days	1
5 days	1
1–12 mo	6
1–3 yr	6
5–10 yr	6
10+ yr	2
Total	22

were 43 instances of combined hypertension and congestive heart failure, nine of hypertension and cerebrovascular accident, and five records of congestive heart failure, cerebrovascular accident and hypertension in the past history of the same patient.

A total of 69 records (27 per cent) revealed a history of *diabetes mellitus* existing from 1 to 40 years. There were 26 additional patients with no known previous history of diabetes mellitus in whom fasting blood sugars were over 150 mg/100 ml, making a total of 95 patients (36 per cent) with diabetes. (Table VIII.)

TABLE VIII

Patients with a History of Previous Diabetes

Duration (years)	Number of patients
1–3	6
5–10	12
10–20	18
20–29	5
30	1
40	2
Unspecified	25
Total	69

There was a history of the regular ingestion of preparations of *digitalis* in 57 patients. Previous use of digitalis was denied by 189, and no information was available in 18. Sixty patients, who had received no previous digitalis preparation, were digitalized in the hospital.

CHIEF COMPLAINT

There were 185 patients (70 per cent) who had a specific chief complaint of pain in the chest including the substernal or precordial regions. The duration of thoracic pain from onset to hospital admission is listed in Table IX. Eighty-nine of 109 patients (82 per cent) for whom exact time intervals were recorded experienced pain in the chest for less than 72 hours' duration, and 75 patients (69 per cent) had thoracic pain of less than 24 hours' duration. Eighty-eight patients (33 per cent) had a chief complaint of dyspnea, and 41 (15 per cent) had a combination of pain in the chest and shortness of breath. Fifteen patients experienced syncope

TABLE IX

Duration of Chest Pain

Duration	Number of patients
Less than 2 hr	22
3–8 hr	32
10–24 hr	21
36–72 hr	14
4–7 days	7
10–21 days	8
More than 21 days	5
Unspecified	76
Total	185

or collapse at the onset. A myriad of chief complaints in the remainder included nausea and vomiting in nine, pain in the abdomen in eleven, and pain in the arm, face, back or leg, headache, weakness, hemoptysis, hematemesis, vertigo, cough, chills and fever, sweating, and swelling of the ankles. Three patients (1.1 per cent) had no chief complaint, and acute myocardial infarction was diagnosed fortuitously after admission to the hospital.

PHYSICAL FINDINGS

Among our patients, 218 (82 per cent) were observed to have a rectal temperature over 100° F during the acute myocardial infarct, and 46 (18 per cent) had no fever. Two of the afebrile patients exhibited hypothermia on the first hospital day with readings of 97° F rectally. (Table X.)

TABLE X

Duration of Fever

Time	Number of patients
No fever	46
Hypothermia	2
Fever on the first hospital day	34
1 day of fever	46
2 days of fever	36
3 days of fever	24
4–7 days of fever	39
More than 7 days of fever	34
Total	261

The normal *pulse* was considered to be between 60 and 100 beats per minute and regular. Tachycardia was observed in 74 patients, bradycardia in 14 patients, and no palpable peripheral pulse on admission in seven patients. In view of the observed coincidence of bradycardia or heart block with acute posterior (diaphragmatic) myocardial infarction, related presumably to the proximity of vagus nerve fibers, the location of the infarct was noted in the 14 cases of bradycardia. There were seven posterior, five anterior and two subendocardial infarcts. There were three cases of complete heart block, of which two were associated with posterior and one with an anteroseptal myocardial infarction. All patients who were pulseless on admission failed to survive.

For the purpose of this study we defined the normal *blood pressure* range between 100/60 mm Hg and 150/90 mm Hg. A definition of normal blood pressure easily becomes ground for dispute. Pickering[8] and Master[9] suggest a rising norm of blood pressure with increasing age, which rise may only reflect increased atherosclerosis. In our series, we adopted the concept that one or more hypertensive blood pressure readings excluded the patient from the normotensive group. Similarly, patients with one or more hypotensive records of blood pressure were not included with normotensive patients. Using these criteria, there were 115 normotensives of whom 61 (53 per cent) died, 114 hypertensives of whom 37 (32 per cent) died, 25 hypotensives of whom 16 (64 per cent) died, and 10 without obtainable blood pressure in whom the mortality was 100 per cent. During the hospital course, a drop of systolic blood pressure of more than 30 mm Hg was observed in 37 of the 114 hypertensive patients, and in four patients there was a drop of blood pressure from hypertensive levels to unobtainable values.

The size of the heart was determined by physical examination and during the convalescent period by x-ray of the chest. The cardiac size was considered to be normal in 30 per cent of the cases on physical examination, and enlarged in 70 per cent. Roentgenographic studies of the chest were performed in 138 cases; the heart was normal in size in 56 per cent and enlarged in 44 per cent.

Distant heart sounds, regarded by some authors as an ominous prognostic sign which occurs predominantly in the older age group of patients with infarction,[10] were recorded in 96 cases (36 per cent) on admission. A gallop rhythm was heard in 12 patients (4.5 per cent) and a pericardial friction rub in 17 (6 per cent). An apical systolic murmur was recorded in 30, an aortic systolic murmur in 16, and an aortic diastolic murmur in two patients.

Pulmonary edema was observed during the examination of the lungs of 30 patients and 14 of these individuals failed to survive. Basal rales were heard in 108 patients (41 per cent) and pleural effusion was noted in 18 cases of which four instances were bilateral, seven on the right side and seven on the left. Wheezes were described in 19 patients and marked emphysema in 8. Normal lungs were found in 50 patients (19 per cent). The heart and lungs were normal by physical examination in 37 patients (14 per cent). Congestive heart failure by physical examination was diagnosed in 52 per cent of the patients.

LABORATORY STUDIES

In 240 patients, determinations of *hemoglobin* levels were recorded. Seventy (29.1 per cent) had a hemoglobin of over 15.0 g/100 ml; 147 (61.2 per cent) had a hemoglobin between 11.0 and 15.0 g/100 ml; 20 (8 per cent) had a hemoglobin between 8.0 and 10.9 g/100 ml; and 3 (1 per cent) had a hemoglobin below 8.0 g/100 ml.

Sixty patients (23 per cent) had a normal total *white blood cell count*, between 5,000 and 10,000 white blood cells per cubic mm. Of these, 28 had a late rise above the initial value of over 2,000 cells per cubic mm with the maximum total count remaining below 10,000, and 13 had more than 70 per cent polymorphonuclear white blood cells on differential count. Nineteen patients had a completely normal unchanged differential and total white blood cell count. Leukocytosis (over 10,000 WBC per cubic mm) was present in 180 patients (77 per cent), of whom 47 had a white blood cell count between 15,000 and 20,000, and 32 had a white blood cell count over 20,000 per cubic mm.

The Wintrobe method of erythrocyte *sedimen-*

tation rate was utilized and values of 0 to 10 for males and 0 to 20 for females were considered normal. Of 215 patients so studied, 19 (9 per cent) had normal sedimentation rates, 6 on two or more determinations; 160 (74 per cent) had elevations, and 36 (17 per cent) had initially normal but subsequently elevated sedimentation rates. Elevation of both white blood cell count and sedimentation rate was recorded in 173 patients, and both were normal on one determination each in three patients (1 per cent).

Urinalysis revealed albuminuria in 108 patients (41 per cent) the magnitude of which in 62 patients was a trace to 1 plus; in 26, 2 plus, in 12, 3 plus, and in 8, 4 plus. Albuminuria was associated with pyuria in 10, with congestive heart failure in 86 patients, with hypertension in 70 patients, and with uremia in 4 patients. There were four cases (1.5 per cent) of albuminuria associated with acute myocardial infarction without apparent other cause. Glycosuria was observed in 70 patients, of whom 25 had fasting blood sugars above 150 mg/100 ml.

A normal *blood urea nitrogen* was found in 86 patients, and an elevated BUN in 66 patients (25 per cent), of whom 22 had levels over 50 mg/100 ml. A *fasting blood sugar* below 80 was discovered in five patients. The FBS was between 80 and 120 mg per cent in 54 patients, between 121 and 149 in 42 patients, and over 150 mg/100 ml in 74 patients, of whom 26 had no previous history of diabetes. A FBS above 150 was considered diagnostic of diabetes mellitus.

Determinations of total *blood cholesterol* were recorded in only 50 patients. There were 16 with values over 250 mg/100 ml (upper limit of normal). In this group there were ten male patients and six female patients (one premenopausal); there were eleven with a previous history of coronary artery disease, nine with a previous history of hypertension, and five with a previous history of diabetes. Four deaths were recorded in the hypercholesterolemic group. Among the 34 patients with normal levels of serum-cholesterol there were 12 deaths.

The heart findings by *x-ray of the chest* were described previously. Pulmonary congestion at the bases was present in 21 (15 per cent). Disease of the right middle lobe was observed in three, pulmonary fibrosis in two, pleural effusion in six, and a substernal thyroid in one case.

Electrocardiographic evidences of transmural myocardial infarction, as signified by progressive T, S-T, and Q wave changes were present in 221 cases and are classified in Table XI. In addition, there were 15 cases of T wave and ST segment changes compatible with subendocardial myocardial infarction. No electrocardiograms were available in 22 cases and normal or nondiagnostic electrocardiograms were present in the records of six patients. There were five patients with combined acute anterior and posterior infarction, of whom four died. Other findings included left bundle branch block in 13, right bundle branch block in 11, changes of right ventricular hypertrophy in 5, of left ventricular hypertrophy in 11. Studies of heart rhythm by electrocardiogram revealed a wandering pacemaker in two, auricular fibrillation in nine, Wolff-Parkinson-White syndrome in two, complete heart block in three, intraventricular block in four, ventricular tachycardia in two, and ventricular extrasystoles in eighteen. (Table XI.)

TABLE XI

Location of Infarct by Electrocardiogram

Anterior	80
Anteroseptal	40
Anterolateral	13
Posterior	71
Posterolateral	10
High lateral	2
Subendocardial	15
Anterior and posterior	5

In view of the relationship of *vitamin C* to connective tissue and tissue healing[49] we observed the results of the administration of ascorbic acid upon healing of infarcted myocardium as reflected in mortality and in the incidence of cardiac rupture. Vitamin C was given to patients in alternate wards. Ascorbic acid in doses of 50 mg daily was given to 108 patients (41 per cent), of whom 31 (29 per cent) died, 9 in less than 48 hours, and 22 in more than 48 hours. No ascorbic acid was given to 156 patients (59 per cent), of whom 84 died (54 per cent), 44 in less than 48 hours, and 40 in more than 48 hours. There were three

cases of cardiac rupture, after two, five, and nine days of hospitalization occurring in patients who received vitamin C.

The results of *anticoagulant therapy* will be elaborated and discussed elsewhere.[1]

HOSPITAL STAY

The duration of hospitalization varied from less than one hour to 80 days; the median was 40 days and the mean 15 days. A significant number of patients, 32 per cent, were hospitalized seven days or less, either because of death, or because of refusal to remain. (Table XII.)

TABLE XII
Length of Hospital Stay

Days	Number of patients
1	36
2	20
3–4	15
5–7	14
8–15	50
18–25	74
28–30	19
31–35	19
40–80	18

TABLE XIII
Incidence of Admission with Myocardial Infarction, Related to Month of the Year

Month	Number	Month	Number
July	18	January	24
August	23	February	16
September	24	March	28
October	19	April	28
November	23	May	23
December	21	June	17

The incidence of admission in relation to month of the year is given in Table XIII. Follow-up studies subsequent to discharge from the hospital were not available.

SURVIVALS AND DEATHS

A total of 140 patients or 53 per cent, survived the acute myocardial infarction. The mortality was 47 per cent (124 patients). Fifty-six deaths occurred within the first 48 hours of hospitalization and 69 patients died more than 48 hours after admission. On the University Medical Division II of Kings County Hospital during the same year, exclusive of patients with tuberculosis, there was a total of 4,791 patients discharged, which included 999 deaths, with an over-all service mortality of 21 per cent.

Autopsies were performed on 65 of the 124 fatal cases (52 per cent), and the findings will be included in a subsequent publication.[3]

"Poor risk" cases, as defined by Russek and Zohman,[11] constituted 77.5 per cent of our series and had at least one of the following findings: (1) previous myocardial infarct; (2) intractable pain; (3) extreme degree of or persistence of shock; (4) significant cardiomegaly; (5) gallop rhythm; (6) congestive heart failure; (7) auricular fibrillation or flutter, ventricular tachycardia, or intraventricular block; (8) diabetic acidosis, marked obesity, previous pulmonary embolism, varicose veins, thrombophlebitis past or present, polycythemia or other states predisposing to thrombosis. Of a total of 204 such "poor risk" patients the mortality was 51 per cent, whereas in the "good risk" group of 60 there were deaths in 20 or 33 per cent.

Discussion

The opportunity to study a large series of cases of acute myocardial infarction within the space of one year is not easily available, and requires a large municipal hospital. Most large series[12,26] of cardiac infarction have been collected over many years during which time changing concepts of therapy of the primary disease, such as the length of bed rest,[47] the treatment of complications, exemplified by anticoagulants therapeutically or prophylactically for thromboembolism, and more recently the use of the cardiac pacemaker[48] for ventricular standstill or fibrillation, may influence the outcome of the illness.

Age: The average age of our patients, 68, is somewhat higher than that of previous series, and may be due in part to a more indigent group of patients who are too old to be included in hospitalization plans and who are products of the increased life span. Such people are attracted to a municipal hospital. In three other

series of 1,031,[13] 572,[14] and 500 cases,[15] the average ages were 59, 60, and 55. Over 91 per cent of our cases were beyond the age of 50, 71 per cent over 60, 36.5 per cent more than 70. Previous studies confirm the age and mortality relationship.[16]

Race: The small proportion of Negroes in this series (1.1 per cent) is of considerable interest in view of their comprising 25 per cent of the total patient population. A lesser incidence of myocardial infarction in Negroes than in Whites has been noted previously. Yater[10] found that only 3.8 per cent of Army personnel on active duty dying of coronary artery disease during World War II were Negroes, whereas the over-all Service percentage during the same period was 10 per cent. Negroes may have a lower diagnostic incidence of myocardial infarction because of less angina and more dyspnea as a presenting symptom.[17] Differences in collateral coronary circulation in the Negro may be explanatory.

Sex: There are more males than females with myocardial infarction in almost all series, with the ratio varying from 2 to 1 to 6 to 1.[18] Wright[13] notes a sex ratio of 1 to 1 among patients with myocardial infarction 80 years of age or older. The incidence of males in this series was 61 per cent as contrasted with the fact that only 45 per cent of the total patient population was male. The majority of our female cases were postmenopausal, in keeping with the older age of the group. This fact may relate the greater relative incidence of female cases to the loss of significant estrogen effect.[19] Important effects of estrogens on blood vessels and blood have been recorded[20] and include general arteriolar dilatation during the week prior to menstruation and thrombocytopenia before and at menstruation. These factors may be part of the protective effect of the menstruating female against myocardial infarction by periodic increased blood flow and hypocoagulability of blood. The decreased incidence of acute infarction in our postmenopausal females may be more directly related to sex differences in lipid metabolism exclusive of significant active estrogen stimulation.

The known predilection of coronary artery disease for Hebrews is confirmed, inasmuch as 63 per cent of our patients were Jewish, and Hebrews constituted only 14 per cent of the total hospital population at that time.

A distinct *familial history* of cardiovascular disease (49 per cent) was observed in our series. Yater[21] found a fourfold higher incidence of cardiovascular disease in the immediate families of those who survived an acute coronary occlusion where a history was obtainable.

Two of our patients had a *cerebrovascular accident* in the week prior to admission. We are reminded that an acute myocardial infarct may be obscured by an evident hemiplegia secondary to decreased cerebral blood flow from shock or congestive heart failure attendant upon the acute myocardial infarction or secondary to emboli originating from mural thrombi following previous infarctions. Dozzi[22] found that 12 per cent of 107 patients with cerebrovascular accidents at autopsy had unsuspected acute myocardial infarcts.

Angina pectoris prior to the myocardial infarction has been variously reported in frequencies of 22 per cent[23] to 73 per cent.[14] According to Doscher and Poindexter,[24] among 3,315 cases in 16 series, the incidence of antecedent angina was 44 per cent. In our series a history of angina was obtained in 148 of 244 cases (61 per cent). The history of previous myocardial infarction in 23 per cent of the patients in this series is identical with that in Wright's series.[13]

Congestive Failure: A great number of our patients, 44 per cent, had a history compatible with congestive heart failure on admission, whereas in a series of 1,001 patients[13] only 15 per cent reported such a history with a death rate of 23 per cent. A diagnosis of congestive heart failure was made in 52 per cent of our cases upon physical examination. The mortality of associated acute myocardial infarction and congestive heart failure has been known to be high, with 55 per cent reported by Billings, Meneely *et al.*[25] and a mortality of 71 per cent of 121 patients with failure observed by Wooten and Kyser.[26]

Hypertension: The relationship of hypertension to myocardial infarction has been considered a close one. We found a history of high blood pressure in 37 per cent of 232 cases, but the validity of this figure is considered doubtful because of the absence of actual blood pressure

readings in most instances. The number of patients with preexisting hypertension has varied in the literature from 35 per cent of 572 cases[14] to 90 per cent of 100 cases.[27] In our series, one or more recordings of blood pressure above 150/90 mm Hg was considered to be hypertension. Using this criterion, a like number of patients, 43 per cent, were normotensive or hypertensive on physical examination. We observed a mortality of 53 per cent in those patients who were consistently normotensive, compared with a mortality of 32 per cent in patients who were hypertensive on admission or at some time during the hospital course. Sigler[28] concluded that hypertension did not have prognostic import in myocardial infarction, although his tables appear to indicate a greater mortality in normotensives. Donald[29] stated that the immediate prognosis of coronary occlusion was better in the presence of hypertension but that the ultimate prognosis was worse; whereas Gross and Engelberg[27] noted no effect of hypertension on longevity. Hypertension may maintain, in the coronary circulation, a higher head of pressure which perfuses ischemic areas of myocardium adjacent to dead tissue, results in less extension of infarction, and improves the immediate prognosis.

The sinister prognosis when *shock* accompanies myocardial infarction[46] was emphasized by our experience. The details will be described subsequently.[2]

The incidence of *cardiac rupture* has been considered to be higher in patients with hypertension than in patients with normal blood pressure.[18,30] Two of our three patients with cardiac rupture had hypertension with the acute myocardial infarction, and the other had a history of hypertension prior to a cerebrovascular accident three years previously.

Diabetes: Diabetes mellitus following myocardial infarction, previously unrecognized, has been noted.[31,32] The high incidence of diabetes mellitus in this series (36 per cent) is consistent with previous reports[33] and has been related to increased coronary atherosclerosis and associated alterations in lipid metabolism. Joslin[34] found that patients with diabetes mellitus of over five years' duration almost always had coronary sclerosis. This relationship is particularly notable in females, whether pre- or postmenopausal.[35] Twenty-six patients with no known previous history or symptoms of diabetes mellitus had fasting blood sugars over 150 mg/100 ml. It is possible that the stress of an acute infarct may have been responsible for the hyperglycemia as a manifestation of latent diabetes.

Pain: Painless myocardial infarction has been reviewed on many occasions and the incidence in various series ranges from 1 per cent[36] to 61 per cent.[37] The appreciation of pain-equivalent symptoms such as dyspnea or breathlessness in coronary artery disease has increased diagnostic acumen. The infrequency of pain with cardiac infarction in the Negro has been mentioned previously. In one study of 70 cases of myocardial infarction without pain[38] previous heart failure, prior myocardial infarction, hypertension, or auricular fibrillation increased the likelihood of a painless cardiac infarct. In our series, congestive heart failure was present in 52 per cent, prior myocardial infarction in 23 per cent, and hypertension in 43 per cent by physical examination. Thirty per cent of our patients experienced no chest pain, and 21 per cent had no pain of any type. Hyposensitivity of the patient, psychosis, extreme shock, infarction of an area of myocardium supplied by a previously occluded coronary vessel, and predominance of pain-equivalents are the explanation for most painless infarcts. Marchand[39] reports an incidence of 67.5 per cent of painless cardiac infarction in psychotic patients, exclusive of sudden deaths. Pain was absent as a presenting symptom in 82.5 per cent of these cases. Evidence of the loss or absence of pain is notable in the 12 cases of sudden death in the above series in which there were four cardiac ruptures and one rupture of the interventricular septum, all painless.

Patterns of pain in myocardial infarction have been, on occasion, interesting and unusual, resulting at times in erroneous diagnoses. One of us (M. M.) has observed a fatal case of myocardial infarction, proved at autopsy, with pain in the left ear as the only symptom, which symptom may have been reflex in origin, being transmitted via the auricular branch of the vagus nerve. Kreines[40] has suggested an association

of the extent of infarction to atypical sites of radiation of pain such as the back and the epigastrium. Epigastric pain, which historically masqueraded as acute indigestion, was noted in 18 per cent of 144 cases in Bean's early monograph.[41] Abdominal pain was a presenting complaint in 11 (4 per cent) of our cases; pain outside the chest was the chief complaint in 9 per cent and included the arms, back, legs, abdomen, face, and head.

Pain in the chest of long duration and thoracic pain without radiation have been associated with a greater mortality according to Behrmann *et al.*[42] In this series, 69 per cent of patients who complained of pain in the chest had it for 24 hours or less and 50 per cent for eight hours or less. This observation would appear to remove pain lasting more than 24 hours as a factor influencing the mortality.

Fever: Prolonged fever with myocardial infarction is not common. The usual temperature course is that of fever of less than seven days' duration. Thirty-four of our patients (13 per cent) had fever more than seven days. This finding is in keeping with the many severely ill patients in this series and may be a reflection of very extensive cardiac necrosis or of a complicating infection such as bronchopneumonia.

Tachycardia: An increase in mortality has been described[14] in patients who display a sinus tachycardia. In the absence of heart failure, shock, or fever, the pulse rate is usually normal.[18] The mortality of patients with sinus tachycardia in our series was 66 per cent.

Blood Findings: A transitory elevation of hemoglobin or hemocrit has been a frequent observation in acute myocardial infarction.[13] We noted a hemoglobin over 15 g/100 ml in 29 per cent of patients during the first 48 to 72 hours after admission to the hospital. Elevated hemoglobin levels were observed to return to normal during the hospital course. A very definite increase in the viscosity of the peripheral blood is notable with rises in hemoglobin levels above 15 g/100 ml.[51] We may speculate that the high hemoglobin level in the peripheral blood is secondary to the "stress"[50] of an acute myocardial infarction; no information is available concerning the coronary artery blood viscosity during the acute phase of infarction.

Uremia was noted by Bean[41] in one-third of 125 cases of acute myocardial infarction and he stated that it was of no prognostic import. We found an elevation of the BUN in 66 patients (25 per cent) in whom it was recorded and values over 50 mg/100 ml in 22 (8 per cent). This elevation may represent the increased incidence of renal arteriosclerosis and arteriolar nephrosclerosis in our age group of patients, or, in some patients, a sequel of hypotension.

Vitamin C: The greater survival rate of those patients in our series who received ascorbic acid is statistically significant,* and encourages speculation regarding the relationship of vitamin C to connective tissue and healing processes of the myocardium. Paradoxically, the three cases of cardiac rupture in this series occurred in patients who were receiving ascorbic acid. We were interested to note that Manchester[43] used vitamin C as a control placebo in evaluating the efficacy of anticoagulants on a long term basis; his results revealed anticoagulants to be more beneficial for survival than vitamin C. Further observation and study will be required to assess any possible role of ascorbic acid in survival of patients with acute myocardial infarction.

Mortality: The high mortality of 47 per cent in this series is not unexpected. The older age of the patients, previously noted, is a factor which decreases the likelihood of survival, inasmuch as older patients often enter the hospital more critically ill with body defenses and spirit weakened by previous disease.[16] Studies in Houston[44] and general experience reveal that patients entering a city or charity hospital with acute cardiac infarction are sicker and more debilitated, with a greater expected mortality, without reflection on resident or attending staffs. Many critically ill patients in our series, found by the police hours after the onset of illness, were then hospitalized; and delay in hospitalization has been cited as a factor in increased death rate from acute myocardial infarction.

The over-all mortality of ward patients was greater than that of private patients in Wright's collected series,[13] and all our patients were ward patients. Good nursing care is an undeniable factor in survival, and in Wright's series[13] of private hospital patients, 22 per cent had special

* Chi^2 is less than 0.01, which is highly significant.

nurses in attendance whereas only 3 per cent of ward patients had special nurses. In our hospital, 4.9 per cent of all ward medical patients had special nurses. The high mortality associated with tachycardia during acute myocardial infarction in our series was significant (66 per cent) inasmuch as 35 per cent of our patients had a rapid heart rate. An appreciable number (13 per cent) of our patients had fever more than seven days, perhaps an indication of extensive cardiac necrosis, with its attendant poor prognosis. The high death rate when congestive heart failure was associated with acute infarction has been discussed, and was 52 per cent in our series. Finally, the application of the "poor risk" criteria of Russek and Zohman[11] or the "pathological index rating" of Schnur[45] revealed that 77.5 per cent of our patients could be classified as bad risks.

Summary

(1) A clinical evaluation of 264 proved cases of acute myocardial infarction in a city hospital during a one-year period is presented.

(2) Previous findings of a greater incidence of this disease in males, Hebrews, patients with a familial history of cardiovascular disease, previous evidence of coronary artery disease or diabetes mellitus are supported.

(3) A very low incidence of acute myocardial infarction in Negroes was observed.

(4) A greater number of older patients was noted in our series than in previous reports.

(5) Painless cardiac infarction was observed in 21 per cent of our patients.

(6) We observed a greater survival rate in patients who were hypertensive on admission or at some time during the hospital course than in normotensives or hypotensives.

(7) The grave prognosis of shock accompanying myocardial infarction is confirmed.

(8) Twenty-nine per cent of our patients had an elevated hemoglobin on admission, which elevation was transient.

(9) We observed three cases of cardiac rupture; these cases received no anticoagulants but were given ascorbic acid.

(10) A significantly greater survival rate was observed in patients who received vitamin C.

(11) The high mortality rate (47 per cent) was attributed to the age of the patients, more critically ill patients, lack of private nursing care, a city hospital ward population, and a high incidence of congestive heart failure, prolonged fever, and tachycardia.

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Surgical Treatment for Endocardial Fibroelastosis or Anomalous Left Coronary Artery*

Four Years' Experience with Poudrage

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IN AUGUST, 1955 we reported our experience with a surgical procedure for endocardial fibroelastosis and anomalous left coronary artery.[5] At that time three cases of endocardial fibroelastosis and one of anomalous left coronary artery were included, with one operative death and a survival of one year or more in the remaining three. It is the purpose of this communication to report on the progress of the original survivors and add our experience with six additional cases.

In the original report we proposed the relatively simple procedure of instilling sterile talc powder into the pericardial sac over the surface of the left ventricle. This was suggested on the theory that anoxia of the left ventricle is the basic difficulty in each of the two conditions. In anomalous left coronary artery the blood supply to the left ventricle is from the pulmonary artery via the aberrant coronary artery, thus perfusing the myocardium with venous blood under low pressure, a situation which obviously would lead to some anoxia of the left ventricle. To us it seems likely that the basic difficulty in endocardial fibroelastosis is a result of obstruction to drainage of blood from the myocardium by the way of the Thebesian, arterioluminal and arteriosinusoidal vessels which are narrowed by the fibroelastic thickening of the endocardium. This view is not universally shared and is thought by some to be due, instead, to interference with heart action by a "constrictive endocarditis," making it grossly similar to the difficulty encountered in constrictive pericarditis.[6] However, if the former concept is accepted myocardial anoxia is the end result of obstruction to drainage with its consequent venous stasis. If, then, both anomalous left coronary artery and endocardial fibroelastosis share a similar pathophysiology of myocardial ischemia, any procedure which might increase arterial blood supply to the left ventricle should increase the efficiency of the myocardium and alleviate the myocardial difficulty encountered in these two conditions. We felt that instillation of sterile talc powder into the pericardial sac over the left ventricle would fulfill this need by stimulating the growth of new blood vessels.

The feasibility of this procedure was strengthened by the report of Thompson and Plachta,[7] which cited their experience in both animals and humans. Their work showed that in experimental animals the instillation of talc in the pericardial sac led to (1) myocardial hyperemia, with dilatation of pre-existing vessels and formation of new ones in the myocardium; (2) foreign-body granuloma between the pericardium and myocardium; and (3) an adhesive granulomatous pericarditis without constriction, through which anastomoses occurred between

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myocardial and extracardiac vessels. Their follow-up on human subjects with cardiopexy up to ten years showed neither tendency to scar formation nor constrictive pericarditis.

For these reasons this procedure was first carried out on an infant with endocardial fibroelastosis in March, 1954. Although we could carry out no experimental work regarding its effect on this anomaly, it was reasoned that the relative simplicity of the operation and the short operating time involved probably made it a safe procedure to perform on this child. It seemed that production of an increased blood supply to the left ventricle would be relatively or even completely harmless should it subsequently prove to be of no benefit for this condition. Furthermore, statistically speaking, the outlook for life was extremely poor without some medical or surgical help. Most of the larger case reports show a mortality rate of at least 90 per cent before two years of age.[1–4]

Review of Original Cases

The essential information in the original four cases previously reported can be found in the composite chart (Table I) representing the ten operated cases. Cases 1 and 3 are those of endocardial fibroelastosis and Case 2 is one of anomalous left coronary artery. These patients are all living and well and none are on digitalis. All seem to be clinically improved in comparison to their preoperative condition.

Case 1 (J.A.) seems to have progressed better, in general, than the other two. He is completely asymptomatic and appears entirely normal in all respects except for heart size. Case 2 (A.E.) developed multiple premature ventricular contractions and cardiac decompensation one year postoperatively, which necessitated resumption of digitalis. The frequency of these premature beats decreased sharply in the subsequent months and digitalis was discontinued eight months later with no further signs of heart failure. He still demonstrates occasional premature contractions but is otherwise symptom-free. Case 3 (N.D.) continues to manifest very mild dyspnea which has persisted in this degree since shortly after operation. Prior to this time her dyspnea was quite marked. Her general improvement may be estimated as moderate and somewhat less than that of her two predecessors. Case 4 (J.M.) died in the immediate postoperative period.

Further postoperative progress of this group as related to weight gain and to heart size or cardiothoracic ratio will be described later under a separate heading with the survivors of the additional group.

Case Histories (Cases 5–10)

Case 5 (W.M.H.). This colored female was first seen at the John Gaston Children's Hospital on November 17, 1953 at the age of four months with cough, fever and dyspnea. Her birth weight was 8 lb, 8 oz and on admission she weighed only 9 lb, 10 oz. She had been ill with an upper respiratory infection for one week and had developed fever and hyperpnea the day before admission.

Physical examination revealed a rectal temperature of 102.8° F, pulse 200 per min and respirations 70 to 80 per min. The heart was enlarged to percussion and there were no murmurs audible. The liver was felt two fingers' breadth below the right costal margin. Her respirations were rapid and labored, there was marked subcostal retraction, and there were bronchial breath sounds bilaterally.

Chest roentgenograms showed the heart to be considerably enlarged, with no definite infiltration noted in the lung fields. The electrocardiogram revealed left ventricular hypertrophy and myocardial damage.

She was promptly digitalized and the following day a soft blowing systolic murmur was heard at the third left interspace. She responded well to initial digitalization and was maintained on five mg whole leaf daily. However, on November 27 she became somewhat worse and the dose was increased to 25 mg per day. Prior to discharge on December 12, 1953 a muscle biopsy was done, which showed no evidence of glycogen storage abnormality.

During the subsequent five months she was readmitted six times, five for sudden episodes of respiratory distress with or without respiratory infection. On one of these occasions she had developed pneumonia and cardiac decompensation. It was learned at this time that the parents had been omitting her digitalis and it was reinstituted. One admission was for severe vomiting and diarrhea, during which she continued to be dyspneic but was well compensated.

On November 30, 1954 an angiocardiogram was done which showed a thick walled, dilated left ventricle with marked delay in emptying of this chamber. No intracardiac shunt was demonstrated. The electrocardiogram revealed combined ventricular hypertrophy.

Because of her continued poor progress, operation was contemplated and on January 9, 1955 (at age 17 months) she was admitted to the Le Bonheur Children's Hospital.

She was operated upon January 12, 1955. The peri-

TABLE I

Summary of Findings in 10 Operated Cases

Case number in order of operation	Name and birth date	Color	Sex	Age at onset of symptoms in months	Age when first seen by us (months)	Presenting or primary complaints	Essential physical findings	Murmur	Heart failure	Cardiothoracic ratio when first seen by us	ECG findings	Date of operation	Age at operation (months)	Date digitalis discontinued	Remarks
1.	J. A. 11-21-53	W	M	3½	4	Vomiting Cough Wheezing		0	+	64	LVH	3-29-54	4	12-4-54	
2.	A. E. 7-22-53	W	M	5	8	Dyspnea Cyanosis attacks Faintness "Angina"	Mild dyspnea	0	+	61	LVH*	4-9-54	8½	1-25-55 (2nd course 11-19-55)	
3.	N. D. 12-12-53	W	F	1	3½	Dyspnea	Anterior chest deformity	+	+ post-operative	61	LVH	6-12-54	6	12-28-54	
4.	J. M. 2-8-54	W	M	2½	8½	Vomiting Dyspnea	Right hemiparesis	0	+	78	CVH	10-29-54	8½		Deceased (11-2-54) All 4 chambers involved. Mural thrombi in apices of right and left ventricles
5.	W. M. H. 7-22-53	C	F	4	4	Severe dyspnea Cough Fever Poor weight gain		±	+	81	CVH	1-12-55	17½	12-16-55	Muscle biopsy negative
6.	J. B. 2-12-54	W	M	7	7	Vomiting Fever Rapid respiration Tachycardia		0	+	70	LVH	6-17-55	16	8-16-55	Auricular appendage biopsy ±
7.	C. L. P. 11-8-54	W	F	½	9	Failure to gain Vomiting	Anterior chest deformity Early closure of fontanelle	0	+	70	LVH†	8-8-55	9		Deceased (8-8-55) Involvement of LV extensive, LA moderate, RA minimal
8.	B. F. C. 9-18-53	C	F	3½	3½	Respiratory difficulty	Dyspnea Subcostal retraction	±	+	70	CVH	9-1-55	24	12-20-55	Muscle biopsy negative
9.	C. W. 2-21-55	W	F	7	8	Vomiting Dyspnea Hoarseness	Pallor Irritability	0	+	69	CVH	11-15-55	9	2-15-56	Developed left hemiplegia postoperative Improved in 6 weeks, little or no residual at 3 months Voice change Deceased 4-22-56 (5 months postoperative)
10.	G. McK. 10-1-54	W	F	5½	16½	Vomiting Pain (colic?) Intermittent fever Poor weight gain	Anterior chest deformity Irritability Profuse perspiration	+‡	+	75	CVH	2-22-56	16½		Deceased LV and LA markedly involved Antemortem muscle biopsy negative

LVH—Left ventricular hypertrophy.
CVH—Combined ventricular hypertrophy.

* Infarction pattern.
† Plus 1st degree A-V block.
‡ Mural systolic only.

cardial sac was opened, the fluid aspirated, and 5 g of sterile talc distributed primarily over the left ventricle. She withstood the operative procedure well and left the operating room in good condition. Her postoperative course was uneventful except for fever which ranged between 100° and 102° F rectally for one week. Physical examination, however, failed to show any signs of infection. She had been receiving digitalis, 25 mg daily, on which she remained for the duration of hospitalization. She was discharged on January 24, the 11th postoperative day.

Follow-up is being maintained at the Children's Heart Clinic of the John Gaston Hospital. She has continued to do well and her dyspnea has subsided. Through oversight, digitalis was not discontinued until December 16, 1955, but no alteration in her general improvement has been noted since it was stopped.

Case 6 (J.B.). This white male infant was first seen at the John Gaston Hospital on September 16, 1954, at the age of seven months, with a history of vomiting and some fever for two days. He had been treated by his private physician with penicillin on two successive days without effect. On admission, the infant was in extremis, pale, slightly dehydrated, and exhibiting extremely rapid, labored breathing. Respirations were 80 and pulse 180 per min. The heart was considerably enlarged to percussion and no murmurs were heard. The liver was palpated 4 fingers' breadth below the right costal margin.

The roentgenograms demonstrated moderate cardiac enlargement, with considerable left ventricular preponderance and pulmonary changes suggestive of decompensation rather than pneumonia. The electrocardiogram showed left ventricular hypertrophy.

The patient was promptly digitalized with some reduction in heart size as demonstrated by a second film taken five days later. His general clinical status was considerably improved within 48 hours and he was maintained on 25 mg digitalis daily.

Clinical diagnosis was endocardial fibroelastosis and he was discharged to the Children's Heart Clinic for further observation. Here he continued to do well. On February 24, 1955 he was readmitted for angiocardiography. This study showed an enlarged left ventricle with increased thickness of the myocardium and delayed emptying of the left ventricle. No right-to-left shunt was demonstrated. A muscle biopsy was negative for glycogen storage disease.

On April 26, 1955 surgery was suggested to the parents, explaining to them our previous experiences and leaving the decision entirely to them. After due deliberation it was decided to operate and on June 15, 1955 he was admitted to the Le Bonheur Children's Hospital.

The poudrage procedure was performed on June 17, 1955 at age 16 months. The pericardial sac was opened, the fluid aspirated and 3 g of sterile powdered talc was dusted over the left ventricular surface. He withstood the operative procedure well and left the operating room in good condition. The tip of the auricular appendage was biopsied in the hope of providing further evidence of endocardial fibroelastosis. Microscopic study revealed some thickening of the endocardial layer, which was approximately twice as thick as the epicardium. With Masson's stain this area contained an excessive amount of fibrous tissue and with elastic stain thick fibers were seen in this layer.

His postoperative course was uneventful except for three days of fever ranging from 101° to 102° F rectally. He had been maintained previously on 25 mg of digitalis daily and was discharged on the eleventh postoperative day on this same dosage.

Follow-up in the Children's Heart Clinic continues to show a general improvement even after discontinuance of digitalis on August 16, 1955.

Case 7 (C.L.P.). This 8½-month-old white female from Kosciusco, Mississippi, was seen in consultation with Dr. Robert Jordan on August 5, 1955. She had originally been referred to Dr. Jordan because of early closure of the anterior fontanelle and a failure to gain weight. At the age of two weeks the infant developed vomiting which was believed at the time to be due to an improper formula. An alteration of the formula was made and the vomiting subsequently stopped. Because of the continued slow weight gain the local physician instituted thyroid therapy which was continued until approximately four weeks before admission. At that time vomiting recurred and was relieved by the discontinuance of thyroid medication. A low-grade fever had been present intermittently for some time prior to admission. The baby weighed 6 lb, 5 oz at birth and only 13 lb, 6 oz on admission at 8½ months of age.

Physical examination revealed a thin, underdeveloped female infant with an obvious anterior chest deformity. There was marked enlargement of the heart to percussion. No murmur or thrill was present.

A routine roentgenogram of the heart showed a marked increase in transverse diameter in the AP view. The apex rested against the left chest wall. Bronchovascular markings were not considered to be abnormal. In the left anterior oblique, the left ventricle greatly overlapped the spine. The electrocardiogram showed a first degree A-V block and definite evidence of left ventricular hypertrophy.

An angiocardiogram revealed no evidence of right-to-left shunt within the heart. The left side of the heart filled appreciably within 4 sec and the left ventricle remained visibly filled through the entire procedure, which extended over a ten second period. There was obvious dilatation of the left ventricular chamber and increased thickness of the left ventricular wall, in addition to delayed emptying of the left ventricle. Clinically, this was felt to be a case of endocardial fibroelastosis and operation was recommended.

On August 8, 1955 the patient was operated upon. During the induction of anesthesia cardiac arrest occurred. The chest was opened rapidly and cardiac massage instituted. Five minims of adrenaline were injected into the heart muscle. The cardiac action returned after approximately 5 min of massage and the remainder of the procedure was carried out as rapidly as possible.

LVH—Left ventricular hypertrophy.
CVH—Combined ventricular hypertrophy.
* Infarction pattern.
† Plus 1st degree A-V block.

A fairly large amount of amber fluid which was present in the pericardial sac was aspirated. Four grams of sterile powdered talc was placed in the pericardial sac and the sac partially closed. At operation it was noticed that the left ventricle was tremendously enlarged and the heart occupied the majority of the left thoracic cavity. The patient left the operating room in fair condition.

The infant had been maintained on digitalis, 25 mg daily, during the preoperative period, but on the morning following operation there was a marked tachycardia of 210 per min. The liver edge was sharp without evidence of enlargement. Digitalis dosage was increased in an attempt to slow the heart rate, not because of any suggestion of cardiac decompensation. The child's respirations were rapid and difficult and because of clinical evidence of extremely poor oxygen exchange tracheotomy was performed. The child breathed well for about three hours following the tracheotomy and seemed to have relatively good oxygen exchange. The heart rate slowed to between 150 and 160 per min but within the two hours preceding death it increased again to 180 per min. The respirations continued to slow and became shallower. Artificial respiration was given but the respiratory rate failed to increase. A reasonably good heart rate and rhythm was maintained until death, the child's primary difficulty appearing to be entirely respiratory. She died 24 hours after operation.

Autopsy: The heart weighed 60 g. The pericardium was adherent to the heart over the area in which the talc was originally instilled. The coronary arteries arose from their normal site in the cusps of the aorta. The left ventricular wall measured 9 mm in thickness as opposed to the right ventricular wall, which measured only 3 mm. Grossly, the endocardial lining of the left ventricle was thick and white and rather extensive. There was moderate involvement of the left auricle and minimal involvement of the right auricle. A coincidental finding was a double ureter from the kidney to the bladder on the left side.

Case 8 (B.F.C.). This Negro female was born at the John Gaston Hospital on September 18, 1953 after a seven-month gestation and weighed 4 lb, 8 oz at birth. Initial physical examination was completely normal and a notation was made that there was no cardiac enlargement and no murmur audible. She was discharged after her weight reached 5 lb.

On January 2, 1954 at $3^1/_2$ months of age she was readmitted to the John Gaston Hospital with a three-day history of respiratory difficulty. Diagnosis by her local physician was upper respiratory infection and she was treated with penicillin. Because she grew worse she was brought to the receiving ward and subsequently admitted. Physical examination revealed rales over the right upper lobe, marked dyspnea and subcostal retraction. The roentgenogram showed right upper lobe infiltration and cardiac enlargement. Electrocardiogram revealed left ventricular hypertrophy.

On the afternoon of admission she developed sudden marked respiratory distress and cyanosis. A loud apical systolic murmur was heard at this time. She was promptly digitalized, with subsequent general improvement and subsidence of cyanosis. She was discharged on January 12, 1954 on a maintenance dose of 10 mg whole leaf digitalis daily.

Follow-up was continued in the Children's Heart Clinic where *no* murmur was heard from February 23, 1954 until February 22, 1955 when a late blowing systolic murmur appeared.

She was readmitted on December 14, 1954 for an angiocardiogram which was technically poor but seemed to show an enlarged left ventricle, with delay in emptying of this chamber. Muscle biopsy was also done and revealed "no abnormal amount of glycogen present by special stain." A diagnosis of endocardial fibroelastosis now seemed even more likely.

She continued to progress reasonably well except for frequent upper respiratory infections (one hospital admission in June 1955 for same) and occasional bouts of dyspnea. However, on August 18, 1955 she developed swelling of the hands and feet and was readmitted the following day. On admission, it was felt she was in low-grade failure and digitalis was increased. At this time a systolic murmur was heard at the apex. The electrocardiogram showed combined ventricular hypertrophy. Because of a lag in weight gain in preceding months and what now seemed to be some deterioration in her general status, operation was decided upon and was performed on September 1, 1955. The procedure and her postoperative course were uneventful. She was discharged on 25 mg whole leaf digitalis on September 10, 1955, her ninth postoperative day.

She is being followed in the Children's Heart Clinic, where digitalis was discontinued on December 20, 1955. Her progress is excellent and she seems to be growing and gaining satisfactorily. The murmur previously described has persisted.

Case 9 (C.W.). This eight-month-old white female, referred by Dr. Hunter Sims of Blytheville, Arkansas, was admitted to the Le Bonheur Children's Hospital on October 19, 1955. According to her history, she was completely normal until three to four weeks before admission, at which time she began to vomit. This had persisted from one to two times daily since onset. She also had a low-grade fever at the beginning and had become somewhat pale and weak since. Respirations seemed to increase but apparently were not labored. Hoarseness developed somewhat gradually about this time and became moderately severe, so that cry was only slightly audible.

Physical examination revealed a slightly pale but fairly well nourished white female, quite irritable and with an extremely hoarse cry. The heart was considerably enlarged to percussion and no murmurs were present. The liver was palpated down to the iliac crest on the right and the umbilicus in the midline.

The roentgenogram showed a moderately enlarged heart in AP view, the C/T ratio measuring 69 per cent. The left ventricle was considerably enlarged in the left anterior oblique view and overlapped the spine by a

marked degree. The electrocardiogram revealed combined ventricular hypertrophy.

The clinical diagnosis at this time was endocardial fibroelastosis and cardiac decompensation. As a result, the patient was digitalized with 300 mg of whole leaf in a two-day period and maintained on 25 mg daily thereafter. She was discharged to be followed as an outpatient until adequate compensation was obtained.

She returned on October 28, 1955. Weight was 18 lb, 13 oz and clinically she seemed improved. There was no further vomiting, her respirations were normal, the liver was down only one finger's breadth and no murmurs were audible. The hoarseness previously noted was still present. A re-check roentgenogram revealed a slight decrease in heart size. Cardiothoracic ratio was now 66.5 per cent.

Angiocardiography was performed on an outpatient basis on November 7, 1955. This revealed no right-to-left intracardiac shunt. There was a marked delay in emptying of the left ventricle and an obvious increase in size of the left side of the heart, involving both the left ventricular chamber and myocardial wall. Inasmuch as a diagnosis of endocardial fibroelastosis was reasonably certain arrangements were made for a poudrage procedure. She was readmitted to the Le Bonheur Children's Hospital on November 14, 1955.

Under general anesthesia 6 g of sterile talc was placed in the pericardial sac, principally in the region of the left ventricle. After closure of the pericardium an additional 4 g of talc was placed in the pleural cavity next to the pericardial sac. The patient withstood the operation very well and left the operating room in good condition. She made an uneventful recovery and was discharged on November 23, eight days postoperatively.

On this same evening, after returning to her home in Blytheville, Arkansas, the patient developed a left-sided hemiparesis which was first noted after the child awakened from a nap. She returned on November 25 and on examination the left hemiparesis was quite evident. Consultation was requested and the neurologist felt that the hemiparesis was essentially complete, although slight movement was obtained in the arm and a little more in the leg on painful stimulation in a gross fashion. There was slight spasticity with hyperreflexia of the neck. The skull was not remarkable and the fundi were within normal limits. It was the impression of the neurologist that this episode was due to a small thrombus or embolus involving a portion of the distribution of the right middle cerebral artery.

Observation was continued and when seen again on January 6, 1956 there was considerable improvement in the weakness of the left side. On February 15, 1956 only slight residual weakness remained. The child was able to walk without difficulty and could use the left upper extremity nearly as well as previously. During the preceding month the marked hoarseness, which had been noted all along, had gradually improved until at this time the voice was nearly normal. Digitalis was discontinued at this visit and when seen again two weeks later she had maintained her previously marked improvement in all systems. The liver was barely palpable. The voice was normal and for practical purposes no evidence of hemiparesis was noted. The only deviation from normal was the appearance of occasional premature ventricular contractions in the electrocardiogram.

She was again seen on April 10, at which time she was doing quite well but gave a history of mild febrile illness one week before. On April 15 she developed a pneumonia which was treated by the local physician with penicillin and streptomycin. However, her response did not seem adequate and she was returned to us on April 17. Physical examination failed to reveal any abnormality other than subsiding pneumonia and she was given achromycin because of the history of poor response to the other antibiotics. There were no signs of failure at this time. The liver was down 2 fingers' breadth and a roentgenogram showed the heart to be approximately the same size as before. Achromycin was continued for four days and she was afebrile for the last two days of treatment. At about that time, however, she began to show some swelling of the eyelids and the following day puffiness of the abdomen. She became somewhat listless on April 22 and the following day was returned to her local physician. In the doctor's office she became considerably worse and vomited a brownish material. Because of the seriousness of her appearance the physician advised hospitalization in Memphis.

En route they stopped in Joiner, Arkansas, where they bought food and drink. While eating, the child suddenly screamed out, developed a jerking of the jaw and very suddenly died.

Postmortem Findings: Autopsy was performed at Blytheville, Arkansas. The heart was grossly enlarged and weighed 150 g with the attached, densely adherent and thickened pericardium. Expected weight for this age is 48 to 56 g. The postoperative reaction was described as a dense epicardial-pericardial-pleural granulomatous reaction, with a left pleuro-diaphragmatic nodule and granuloma formation. (This latter reaction obviously was the result of migration of the talc instilled in the pleural cavity adjacent to the pericardial sac, which was done in an attempt to obtain greater vascularization.) There was marked dilatation and hypertrophy of the left ventricle and moderate dilatation and hypertrophy of the right ventricle. The walls measured 14 and 9 mm, respectively. The endocardial fibroelastic reaction involved the left ventricle and auricle and to a lesser degree the right auricle. A ductus was present but not patent. Normal coronary ostia were found arising from behind the aortic valves.

The lungs showed pulmonary congestion, edema and bronchopneumonia and there was visceral congestion with hepatosplenomegaly. The brain showed an old cerebral infarction over the right cortex and outer portion of the parietal lobe, corresponding to the distribution of a branch of the right middle cerebral artery. No gross vascular thrombus was demonstrated.

Microscopic Report: Multiple microscopic sections of the heart showed a dense layer of fibroelastic tissue lining

the left ventricle and both auricles, with a thinner layer in the right ventricle. On the epicardium of the right and left ventricles there was a relatively dense layer of vascular connective tissue, with a similar layer between the pericardium and both lungs. Numerous blood vessels were seen within the epicardial-pericardial-pleural foreign body membranes. These blood vessels were composed of endothelium but no elastic or muscular components within the walls. In the connective tissue layer were many irregular rectangular crystals (talc) found loose and within giant cells.

Case 10 (G.A.McK.). This 16½-month-old white female, referred by Dr. A. N. Evans of Alexandria, Louisiana, was admitted to the Le Bonheur Children's Hospital on February 19, 1956 with a history of having been well and apparently normal until she was 5½ months of age. At that time she developed frequent bouts of vomiting, "attacks of pain" which resembled colic, and intermittent fever of 103° F rectally. Until the onset of symptoms her weight gain had apparently been satisfactory and she weighed approximately 13 lb at that time. Since then the appetite had decreased and the weight gain slowed considerably so that in the subsequent 11 months until admission here she had gained only 5 to 6 lb (19 lb on admission). The private physician had detected cardiac enlargement on routine roentgenogram during investigation of her new complaints and she was referred at that time to Charity Hospital in New Orleans, where further investigation was made, including a muscle biopsy to rule out glycogen storage disease. She was returned to her private physician with a diagnosis of endocardial fibroelastosis.

Physical examination revealed a thin, underweight female who was quite irritable and perspiring profusely. There was some anterior chest deformity, a little more evident on the left than the right. A few scattered rales were heard in the left chest. The heart was considerably enlarged to percussion, dullness extending into the left axilla. No murmur was heard over the anterior chest, but there was a moderately loud, blowing, systolic murmur heard posteriorly best at the tip of the scapula and medially to the vertebral column. There was a third heart sound at the apex with a suggestive gallop rhythm. The liver was palpable 1½ fingers' breadth below the right costal margin and the tip of the spleen was palpable on the left.

Roentgenograms showed the heart in the AP view to be considerably enlarged. Transverse diameter of the heart measured 11.3 cm and the internal diameter of the chest, 15.0 cm, giving a cardiothoracic ratio of 75 per cent. There was a slight increase of bronchovascular markings in the right hilum. The right anterior oblique view showed considerable posterior deviation of the esophagus, particularly in the region of the left auricle and in the left anterior oblique the left ventricle overlapped the spine by a considerable margin. The heart was grossly enlarged in this diameter also. Angiocardiograms were done which showed no evidence of right-to-left intracardiac shunt. The right auricle, ventricle and pulmonary vessels filled completely by two

Fig. 1 Case 10. The posterior wall of the heart has been cut and reflected upwards revealing the smaller right ventricular cavity (R.V.) and relatively large left ventricular chamber (L.V.). The thickness of endocardium lining the left ventricle is best seen along the cut edge of the septum (arrow).

to two and one-half seconds. The left auricle began to fill by five seconds and filling of the left side was still marked by the end of the series (10 sec). The left side was found to be considerably dilated, the left ventricle alone being quite as large as an average heart in its entirety for this age.

Electrocardiogram showed left ventricular hypertrophy.

Because of the clinical diagnosis of endocardial fibroelastosis and in spite of the poor risk it was decided to attempt the poudrage procedure. This was performed on February 22, 1956. Cardiac arrest was encountered immediately upon opening of the pericardium but after 45 minutes of cardiac massage and calcium chloride injection the heart action improved. Sterile talc powder was then instilled into the pericardium and the wound closed. At the time the patient left the operating room cardiac action was good and her color and respirations fair. However, 2½ hours later there was a sudden cessation of heart beat and respirations and no response to artificial stimulation, adrenalin, caffeine and calcium chloride.

Autopsy: Examination revealed a grossly enlarged heart weighing 150 g as opposed to a normal of 48 g for this age. There was marked thickening of the endo-

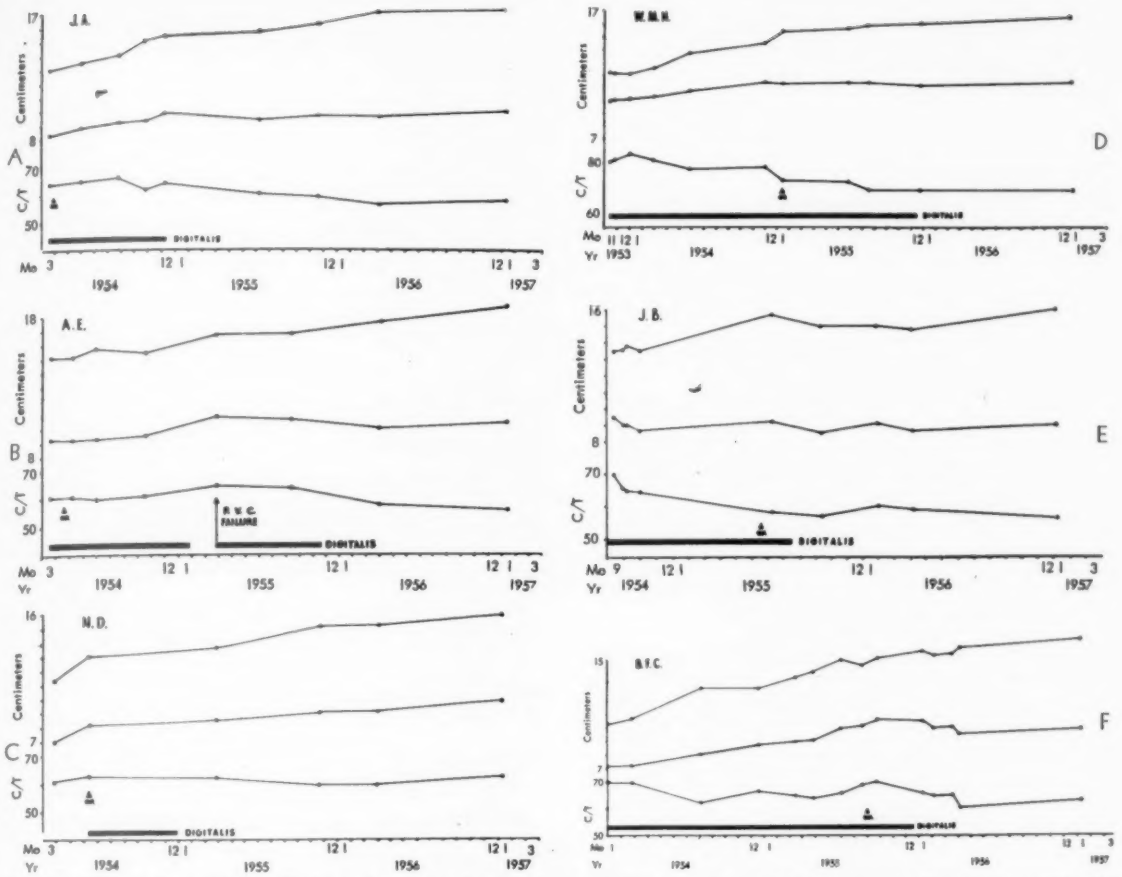

Fig. 2. Heart size and cardiothoracic ratio of surviving cases. In each graph the upper line represents the internal thoracic diameter in centimeters, the middle line represents the transverse diameter of the heart in centimeters and the lower line shows the cardiothoracic ratio in percentage. The heavy black line represents the period during which the patient was on digitalis. The point marked O.P. represents the date of operation.

cardium lining the left ventricle and left auricle. The contrast is strikingly demonstrated in Figure 1 where the thickness of the endocardium is readily seen along the cut edge of the ventricular septum.

Progress as Measured by Heart Size and/or Cardiothoracic Ratio

In all of the survivors there has been some reduction in heart size and/or cardiothoracic ratio (see Fig. 2). The degree of reduction in some instances is not striking but it is obvious on the graphs that in none of the cases has the C/T ratio significantly increased following operation. Furthermore, actual heart size has either decreased or shown a tendency to increase at an insignificant rate.

Case 1 (*J.A.*). There was slight increase in C/T ratio for the first five months postoperatively followed by a rather steady decrease in the subsequent 29 months from a high of 66 per cent to a low of 57.5 per cent (Fig. 2A). This is closely correlated with an absolute increase in heart size for the first eight months postoperatively after which no further increase was noted for the subsequent 25 months. During this time the patient had been off digitalis.

Case 2 (*A.E.*). This patient's course was complicated by the advent of decompensation two months after discontinuance of digitalis. His heart size and C/T ratio were obviously increased during heart failure and decreased while on digitalis (Fig. 2B). If one eliminates the measurements during the second period of decompensation the transverse diameter of the heart increased only slightly from the time of

operation. With the normal rate of increase in thoracic diameter, this has resulted in a stationary C/T ratio.

Case 3 (*N.D.*). There was a rather sharp increase of 1.2 cm in heart size in the $2^1/_2$ months preceding operation after which the rate of increase was decidedly slower, measuring approximately 2 cm increase in size over the subsequent 32 months (Fig. 2C). The C/T ratio has continued in about the same degree throughout, measuring 60–63 per cent.

Case 5 (*W.M.H.*). This case demonstrated an increase in the transverse diameter of the heart in a rather steady line to the time of operation after which there was a levelling off to measurements around 11.5 cm (Fig. 2D). The C/T ratio has decreased steadily although this started early and the operation cannot be given credit for any added rate of decline. It does seem significant however, that no increase in heart size has occurred since operation.

Case 6 (*J.B.*). This patient showed a decrease in heart size in the first two months of observation which can be attributed to compensation by digitalis and no appreciable increase in transverse diameter of the heart following surgery (Fig. 2E). C/T ratio in this instance also has remained at a considerably low level (between 57 and 60 per cent in the initial period of observation). The rate of decrease was not as easy to visualize since no x-rays were obtained in the $7^1/_2$ months prior to operation.

Case 8 (*B.F.C.*). This child demonstrated a rather steady increase in transverse diameter of the heart to a point approximately one month postoperatively after which there was a definite, although slight, decrease in measurement (Fig. 2F). At the same time there was a decrease in C/T ratio although difficult to evaluate in terms of the preoperative ratio.

Case 9 (*C.W.*). Not enough time has elapsed since operation to warrant any definite conclusions regarding heart size and C/T measurements. However, it can be stated that the C/T ratio dropped from a preoperative measurement of 69 per cent to 66 per cent $2^1/_2$ months postoperatively. This is again insignificant but measurably lower after operation.

Progress as Determined by Weight Gain

In general, it might be stated that in all of the survivors there was a definite reduction in development as related to weight in the preoperative period (see Fig. 3). All fall below the 16th percentile on the Iowa State grid. All show a fairly marked weight lag for a short time postoperatively after which in most cases there was a decided increase in growth curve, although in only one (J.A.) did postoperative weight gain reach the 16th percentile line.

Case 1 (*J.A.*). On the birth to twelve month graph (Fig. 3A) it is obvious that this child's weight gain was well below the 16th percentile preoperatively but within three months after operation he had reached the 16th percentile and eight months postoperatively had reached the median line. Thereafter he has demonstrated a tendency to exceed the median as evident on the smaller graph.

Case 2 (*A.E.*). In the first two months this patient's weight curve falls away from the 84th to just above the 16th percentile, and by the immediate preoperative period has fallen considerably below the 16th percentile (Fig. 3B). Thereafter the curve shows a slight increase and by two years postoperative has approached even closer to the 16th percentile line as seen on the smaller graph.

Case 3 (*N.D.*). This patient demonstrates the poorest weight gain of all (Fig. 3C). There is a decided lag, however, in the immediate preoperative period and a slight acceleration postoperatively. In nearly two years from the time of operation she has still not reached the 16th percentile. Family characteristics may have some bearing on this particular case since both the mother and father are relatively short adults.

Case 5 (*W.M.H.*). This patient demonstrates on the birth to 12 month graph a decided fall away from the 16th percentile (Fig. 3D). Within six months postoperatively she has shown a definite increase toward the 16th percentile and by a year postoperatively has closed the deficit considerably.

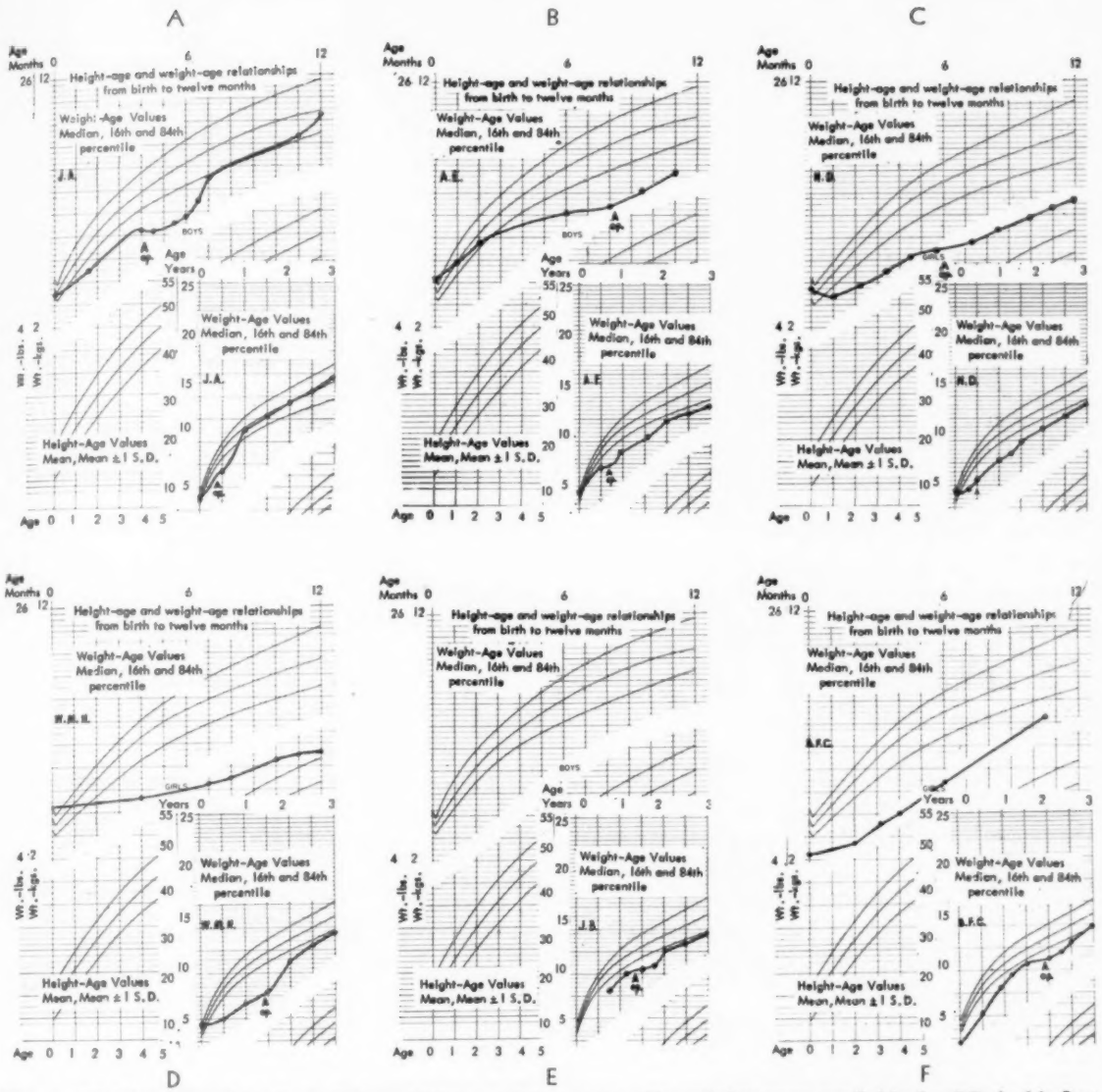

Fig. 3. Weights plotted on Iowa State grid for surviving cases. No weights were available for J.B. in his first year. In each set of graphs, the upper graph shows the weight-age growth curve during the first 12 months of life, and the lower right graph during the first three years. Point O.P. signifies the date of operation.

Case 6 (*J.B.*). Unfortunately, no accurate weight measurements could be obtained on this child for the first year of life (Fig. 3E). On the year graph, however, it is obvious that the weight curve has sharply increased in the nine months postoperatively until his weight at two years has reached almost the 16th percentile curve.

Case 8 (*B.F.C.*). On the birth to one year graph it is apparent that this child's weight curve is considerably below the 16th percentile but does show a tendency toward reaching this line by the end of the first year (Fig. 3F). On the yearly graph it becomes obvious that her weight gain was not persistent and because of the fact that her progress was not persistent operation was resorted to. In the subsequent six months from operation a definite increase in weight curve is again noted but more time will be necessary to determine how persistent this gain will be.

Case 9 (*C.W.*). The time interval since operation in this patient was too short to draw any conclusions on a weight graph. However, her weight had increased from 19 lb before opera-

tion to 21 lb two weeks before death. Other evidences of improvement can be derived from her case history.

Discussion

First, it should be clarified that the cases which we are reporting are those we would consider primary endocardial fibroelastosis, differing from the fibroelastosis which is found in association with certain types of congenital heart lesions. Those instances in which a thickened endocardium is associated with other defects generally demonstrate a patchy distribution and appear to have little or no effect on the symptomatology or fatal outcome of the individual. The cases of primary endocardial fibroelastosis exhibit no additional abnormalities to explain the child's demise. The etiology in these two conditions probably is not the same; however, it is beyond the scope of this paper to argue the pros and cons of the numerous etiological considerations which have been advanced.

We must admit that our biggest problem is that of diagnosis, not so much in suggesting the likely possibility but proving the diagnosis without question. We have assumed that the finding on angiocardiography of a large, thick-walled left ventricle which demonstrates delayed emptying, in an infant with electrocardiographic and x-ray evidence of left ventricular hypertrophy and a history of reduction in weight gain, vomiting and dyspnea after an initial normal newborn period, adds further credence to this diagnosis. We had thought that biopsy of the auricular appendage might confirm the diagnosis at the time of surgery but further consideration makes one realize that the left auricle need not necessarily be involved and furthermore, the mere presence of a thick endocardium does not necessarily prove a primary endocardial fibroelastosis.

The natural course of the disease must be taken into consideration when evaluating any possible postoperative benefits. One cannot deny, however, that all our surviving patients demonstrated general improvement without the necessity of digitalis which had been the only therapy which helped previously to extend life. Neither can one deny that there is some improvement, and in a few cases considerable increase, in the weight curve as plotted on the Iowa State grid. Also, it is obvious that there has been some decrease in absolute heart size, C/T ratio or both in all of our survivors. With all survivors showing these improvements it seems most likely that this is not due to chance alone and if it be attributed to sheer coincidence it is certainly stretching coincidence to a maximum.

The loss of one of our survivors (case 9) did much at the time to dampen our enthusiasm but with continued good progress in the remaining six we are still hopeful that the procedure has merit. That six out of seven survivors are still living two and one-half to four years after surgery and all have been off digitalis for well beyond two years in itself is encouraging. Furthermore, all survivors now being four to four and three-fourths years of age seems hopeful for a condition carrying so high a mortality before the age of two years.

Summary and Conclusions

(1) Ten cases are presented which have been operated for either anomalous left coronary artery (case 2) or primary endocardial fibroelastosis using the poudrage technic previously reported by us.

(2) A four-year follow-up of the three survivors from our first report is included. The subsequent survivors range from two and one-half to over three years postoperative.

(3) All survivors (six cases) are clinically well without benefit of digitalis during the past two to three years.

(4) Improvement with respect to weight curve (Iowa State grid) and heart size and/or cardiothoracic ratio is demonstrated.

(5) It is felt that considerably more time is necessary for absolute proof of the merit of this procedure but with up to four-year survival associated with general clinical improvement in our survivors we are quite enthusiastic that the procedure is beneficial.

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Clinical Comparison of Six Digitalis Preparations by the Parenteral Route*

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SEVERAL digitalis preparations are in use and various claims are currently made in regard to the differences of their action. However, exact clinical comparison is scanty,[1,4,6,12,17,18] so that the physician usually relies either on animal experimentation, obviously inadequate, or insufficient clinical data. For this reason, it was considered advisable to undertake a new clinical study.

THE VARIOUS DIGITALIS GLYCOSIDES

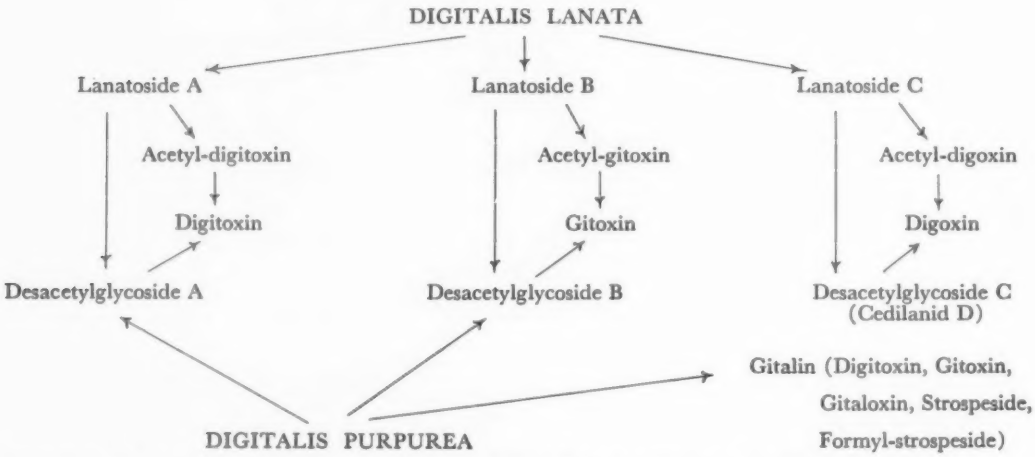
There are two main digitalis plants, *digitalis purpurea* and *digitalis lanata*. Their main glycosides, respectively isolated by Cloetta,[14] Stoll[13] and Smith[19] are digitoxin, gitoxin and digoxin (Table I). As gitoxin has little cardiac action, the other two were an obvious selection for our study. However, several studies have been made with *acetyl-digitoxin α* (an acetylated compound of digitoxin) and with either *lanatoside C* or its deacetylated compound. Therefore, investigations were extended to them. Furthermore, the amorphous compound *gitalin* and the complex of glycosides of strophanthus (*ouabain*) were selected on account of the many clinical studies which have been made with them.

The chemical names, commercial preparation and purity of the drugs used in this study are presented in Table II.

MATERIAL AND METHOD

The present study was based on the observa-

TABLE I



* From the Division of Cardiology of The Chicago Medical School at Mount Sinai Hospital.

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TABLE II
Content and Source of Commercial Preparations

	Commercial preparation	Content (%)	Glycoside	Plant of origin
1.	Digitaline nativelle	96	Digitoxin	D. purpurea
2.	Lanoxin (Burroughs Wellcome)	96–98	Digoxin	D. lanata
3.	Cedilanid D (Sandoz)	96–98	Deacetyl-lanatoside C	D. lanata
4.	Gitaligin (White) (gitalin)*	11.1 13.3 10.6 4.5 8.5	Digitoxin Gitoxin Gitaloxin Strospeside Formyl-strospeside	D. purpurea
5.	Ouabain (Arnaud)	96–98	Complex of glycosides	Strophanthus gratus
6.	Acylanid (Sandoz)	96–98	Acetyl-digitoxin α	D. lanata

* According to recent studies of Haack *et al.*[8]

tions made in 162 cases, treated with different cardiac glycosides. The age distribution was as follows:

21 to 30... 1	61 to 70...54
31 to 40...11	71 to 80...44
41 to 50... 6	81 to 90...10
51 to 60...36	

The average age of the total group was 65 years. There were 101 male and 61 female patients.

One hundred sixty-two patients were suffering from *heart failure*, while 24 were in a control group which included old people without heart failure. One hundred twenty-one cases had sinus rhythm while 15 had atrial fibrillation. The distribution of cases according to the different heart diseases was as follows:

Coronary heart disease	76
Hypertensive heart disease	50
Rheumatic heart disease	23
Cor pulmonale	9
Myocarditis	2
Syphilitic heart disease	2

All patients were treated in bed except for a small group of 12 patients who were treated in the outpatient department.

The total number of patients was divided into six groups of 21 each and a different glycoside (or mixture of glycosides) was given to each of these groups.* Only patients who had not received any digitalis preparation for at least 14 days were selected.

The plan of digitalization was made with the program of a fairly rapid digitalization (two to three days) and the patients were followed for seven days. After this period, digitalization was continued by the resident according to his judgment. The dosage of the cardiac glycosides is in Table III. In the first two days, digitalization was based strictly on the doses of Table III. From then on, it was based on the indicated dosage if clinical judgment indicated that it was advisable to do so. For example, the dose was increased or decreased in a few cases. In some, digitalization was discontinued altogether because of toxic manifestations.

One hundred twenty-five cases received the drug by intravenous injection, while thirty-five received it by the intramuscular route. It was

* A seventh group of 10 cases was treated with lanoxin in reduced dose.

TABLE III

Dose of the Cardiac Glycosides for Each Day of Treatment (mg)

Glycoside	1st day	2nd day	3rd day	4th day	5th day	6th day
Digitaline nativelle (digitoxin)	0.8	0.4	0.4	0.3–0.2	0.2	0.2
Acylanid (Sandoz) (acetyl-digitoxin)	0.8	0.6	0.6	0.4	0.4–0.2	0.2
Lanoxin (B.W.) (digoxin)†	1.5 (1)	0.75 (0.5)	0.75 (0.5)	0.5	0.5–0.25	0.25
Cedilanid D (Sandoz) (deacetylated cedilanid)	1.5	0.6	0.4	0.4	0.4	0.4
Gitaligin (White) (gitalin)	3	2	1	1–0.5	0.5	0.25
Ouabain (Arnaud)	0.5	0.5	0.5	0.25	0.25	0.25

† The figures in parentheses indicate the doses of an alternate series of 10 cases.

ascertained that only digitoxin could be administered by this route without causing intolerable pain. Therefore, out of the 35 above-mentioned cases, twenty-five received digitoxin. As the effect was similar to that of intravenous treatment, these cases were not separated from the others.

In general, the drug was administered in a single daily injection, the exception was ouabain, which was given in two daily injections of 0.25 mg at about 12-hour intervals in the first three days. Preliminary tests with larger doses of ouabain (0.75 mg per day) or 0.5 mg in a single injection were followed by evidence of toxicity (premature contractions, ventricular tachycardia, nausea) and were subsequently discontinued.

Recorded Data: The following data were recorded:

(1) Symptoms, pulse, respirations, blood pressure, and physical data pertaining to the heart, lungs, liver, subcutaneous tissue—daily.

(2) Electrocardiogram—before, on third* and seventh day.

(3) Venous pressure and circulation times (arm-to-lung with ether, arm-to-tongue with decholin)—before, on third* and seventh day.

(4) Heart size (P-A chest film) before and on the seventh day.

Rating: Rating of improvement was made on the basis of the collected data as follows:

(1) *Pulse Rate:* Deduct final rate (end of six days) from initial rate.
Example: 110 − 80 = 30

(2) *Rhythm:*
- (a) If initially irregular (extrasystoles or atrial fibrillation) and becomes regular (sinus rhythm) = 30
- (b) If initially irregular (see above) and later it is still irregular but slower = 10
- (c) If initially irregular (extrasystoles plus fibrillation) and later there is only fibrillation = 10
- (d) If initially regular and it becomes irregular *detract 30* = −30
- (e) If no change = 0

(3) *Respiration:* Deduct final rate from initial rate.
Example: 24 − 16 = 8 or vice versa (negative figure)

(4) *Circulation Times:* Deduct seconds of arm-to-lung plus arm-to-tongue now from same data initially.

* These data were recorded on the 3rd day only in one-third of the cases.

Example:

Arm-lung	10	Arm-lung	8
Arm-tongue	25	Arm-tongue	20
	35		28

35 − 28 = 7

(5) *Heart Size:* Deduct long diameter plus broad diameter *now* in mm from those initially found.

Example:

long diameter	180
broad diameter	140
	320
long diameter	160
broad diameter	130
	290

320 − 290 = 30

If opposite = negative figure

(6) *Venous pressure:* Deduct present venous pressure from initial venous pressure in cm water.

Example: 30 cm − 20 cm = 10

(7) *Toxicity:* If nausea or other toxic phenomena are present, deduct 10 points (no interruption of therapy) or 20 points (drug had to be stopped).

(8) *Rapidity:* If most changes took place during the first three days, 10 points added (rapidity).

(9) *ECG changes:* The graduation of the changes in the ECG was based on an arbitrary scale in which:

(a) S-T depression = 1 mm	= 10
= 2 mm	= 20
= 3 mm	= 30
(b) P-R prolongation	= 10
(c) Occasional ventricular extrasystoles	= 10
(d) If bigeminy	= 25
(e) Slight shortening of Q-T	= 10
(f) Severe shortening of Q-T	= 20

These arbitrary units (a − d) were *subtracted* because they were considered as revealing possible myocardial damage. The units (e) and (f) were not subtracted because they merely indicate digitalis effect. As an opposite opinion has been advocated, a double final rating was made, with and without ECG rating.

Example:

Rate	40
Rhythm	0
Respiration	8
Heart size	24
Venous pressure	39
Circulation times	18
Rapidity	10
Toxicity	0
ECG	(−20)
	119

Results

DIGITOXIN

The distribution of cases was as follows:

Coronary heart disease	9
Hypertensive heart disease	9
Rheumatic heart disease	2
Myocarditis (etiology unknown)	1
Total	21

Analysis of the data revealed the following findings:

Pulse: The reduction of the pulse rate was of a moderate degree, with an average of 14 beats for the total group at the end of treatment. Cases with atrial fibrillation presented a greater reduction.

Venous Pressure and Circulation Times: Both showed a significant diminution at the end of the treatment with an average of 70 units.

Onset of Improvement: This usually started either on the second or third day.

Reduction of Heart Size: This averaged 3.2 cm.

ECG Changes: Digitoxin showed the most severe degree of changes, consisting of moderate to severe depression of the S-T segment, T wave changes, increase of the P-R interval, and at times the appearance of ventricular extrasystoles. An average of 53 units (negative) was found at the end of the sixth day.

Toxicity: Toxic manifestations were extremely rare. Nausea appeared at the end of the treatment in two cases. No other toxic phenomena were noted.

Special Remarks: In one case with first degree A-V block, the drug was given without an increase of the block. One case developed a posterior infarction during treatment. However, this fact cannot be attributed to therapy. A case with myocarditis responded well to the treatment.

ACETYL-DIGITOXIN

The distribution of cases was as follows:

Coronary heart disease	12
Hypertensive heart disease	7
Rheumatic heart disease	2
Total	21

Analysis of the data revealed the following findings:

Pulse: The average reduction in pulse was smaller than with the other glycosides, with an average of 6 beats for the total group. Cases with atrial fibrillation showed a greater reduction.

Venous Pressure and Circulation Times: Both showed a significant reduction at the end of the treatment. This was equal to that caused by digitoxin, with an average of 70 units.

Onset of Improvement: This was usually on the third or the fourth day, later than with digitoxin.

Reduction of Heart Size: This was significant and equal to that obtained with digitoxin, with an average of 3 cm at the end of treatment.

ECG Changes: These were minimal, in contrast with the results of digitoxin. They consisted of a slight depression of the S-T segment in five cases.

Toxicity: No toxic manifestations appeared, with the exception that two patients complained of loss of appetite at the end of treatment.

Special Remarks: Three patients complained of pain in the arm during the intravenous injection.

DIGOXIN

The distribution of cases was as follows:

Syphilitic heart disease	—	1
Coronary heart disease	7	5
Hypertensive heart disease	9	2
Rheumatic heart disease	4	2
Cor pulmonale	1	—
Total	21	10*

* Alternative series with reduced dose.

Analysis of the data revealed the following findings:

Pulse: The reduction of the pulse was fair with an average of 12 beats for the total group at the end of the treatment. Patients with atrial fibrillation showed greater reduction. However, after excluding the patients who interrupted treatment, the average drop rose to 25. The alternative series had an average drop of 30.6, the highest of the series.

Venous Pressure and Circulation Times: Both diminished significantly with an average of 70 units (*equal to those of digitoxin and acetyl-digitoxin*).

Time of Improvement: The onset of clinical improvement usually took place on the third, sometimes the fourth day.

Size of the Heart: The reduction in size was 2 cm for the first group (larger dose), and 0.7 cm for the second (smaller dose).

ECG Changes: Rather significant changes were observed consisting of depression of the S-T segment, changes of the first part of the T wave, and occasional ventricular extrasystoles.

Toxicity: Out of 21 patients receiving the larger doses, nine showed toxic phenomena consisting of nausea, vomiting, visual disturbances, or ventricular extrasystoles. In one case, sudden death occurred on the 3rd day shortly after the injection of 0.5 mg (this had brought the total to 1.75 mg in three days). In eight patients, the treatment was interrupted because of the above reasons (in five, on the third day; in two, on the fifth day; in one, on the fourth day). *Out of ten receiving smaller doses, none developed toxicity.*

General Improvement: Improvement was good with an average of 54 units. If the ECG changes were excluded, the rating was 69.

Special Remarks: One patient with first degree A-V block developed atrial fibrillation before the end of treatment. One patient died suddenly shortly after the 3rd injection (total of 3.25 mg in four days). She had previously suffered from ventricular extrasystoles. Another patient died suddenly on the 6th day after receiving 3.5 mg in five days (reduced dosage). One patient developed a posterior infarction during treatment. Three patients received the drug following recent myocardial infarction and responded well.

CEDILANID D

The distribution of cases was as follows:

Coronary heart disease	11
Hypertensive heart disease	6
Rheumatic heart disease	2
Cor pulmonale	2
Total	21

Analysis of the data revealed the following findings:

Pulse: The reduction of the pulse was one of the highest among all glycosides with an average decrease of 27 beats/min at the end of treatment.

Venous Pressure and Circulation Times: The diminution was of a moderate degree with an average of 50 units (equal to those of gitalin and ouabain).

Onset of Improvement: The onset of improvement was usually on the 3rd day, occasionally on the 2nd.

Size of the Heart: The reduction in the size was of minimal degree, and the lowest of all the glycosides, with an average of 0.4 cm.

ECG Changes: These changes were minimal, were noted only in a small number of cases, and consisted of minimal S-T depression. The majority of cases did not show any change.

Toxicity: Cedilanid had the lowest incidence of toxic reactions of all glycosides. Only one patient lost his appetite at the end of treatment.

General Improvement: This was moderate, having an average of 50 units.

Special Remarks: One patient with complete A-V block (rate 36) received the total dose without complications or further reduction of rate. One patient developed a 2:1 A-V block at the end of treatment, which disappeared five days after discontinuation of the drug.

GITALIN

The distribution of cases was as follows:

Coronary heart disease	11
Hypertensive heart disease	6
Rheumatic heart disease	2
Cor pulmonale	2
Total	21

Analysis of the data revealed the following findings:

Pulse: The reduction of the pulse was of moderate degree with an average of 9 beats/min for the total group.

Venous Pressure and Circulation Times: The reduction of both was moderate with an average of 50 units in the total group.

Onset of Improvement: The onset of improvement was usually at the third day.

Size of the Heart: The reduction in the size was small, with an average of 1.5 cm in the total group of cases.

ECG Changes: Gitalin produced only a slight depression of the S-T segment in some cases. No other abnormalities were noted.

Toxicity: The toxicity of gitalin was moderate. However, 4 cases presented evidence of toxicity (nausea, vomiting, ventricular extrasystoles). Two of them had cor pulmonale.

General Improvement: In terms of units, general improvement was moderate, having an average of 45 units.

Special Remarks: Ventricular extrasystoles, present in 4 cases before treatment, disappeared during the administration of the drug. In two cases, substernal pain developed after the injection.

OUABAIN

The distribution of the cases was as follows:

Coronary heart disease	14
Hypertensive heart disease	3
Rheumatic heart disease	1
Cor pulmonale	3
Total	21

Analysis of the data revealed the following findings:

Pulse: A moderate degree of reduction appeared at the end with an average of 10 beats/min.

Venous Pressure and Circulation Times: Ouabain reduced these data in a moderate degree with an average of 50 units.

Onset of Improvement: There was the fastest onset of improvement, usually starting the second day, but occasionally on the first day of treatment.

Size of the Heart: The reduction in size was of a moderate degree, with an average of 0.8 cm for the total group.

ECG Changes: These changes were moderate, and consisted of slight S-T depression.

Toxicity: Toxic manifestations were rather high. Four cases had nausea and vomiting, and ventricular extrasystoles.

The General Improvement: In terms of units this was moderate with an average of 20 units.

Special Remarks: One case received the drug after a recent infarction and responded well. One patient died suddenly immediately after an injection of 0.5 mg. Two cases with cor pulmonale showed early evidence of toxicity.

CONTROL GROUP

Twenty-four patients without evidence of failure were studied as controls. They were of an average age of 65, similar to the groups of treated patients. These patients were selected among the residents of a Home for the Aged, and the main complaint was arthritic pain. They were given digitoxin, digoxin, and gitalin.

The size of the heart did not change in 18 patients. The other six patients, who presented no other obvious clinical evidence of failure but had an enlarged heart, had a reduction of heart size after treatment. No toxic phenomena took place. The pulse reduction ranged from 2 to 6 beats in 16 cases, and showed no change in the other eight.

General Remarks

Patients with more rapid pulse rate (particularly in the presence of atrial fibrillation) showed the greatest reduction following digitalization.

Four cases developed myocardial infarction during the treatment, and three experienced substernal pain. Even though digitalization may have been only a concurrent cause, it is impossible to deny the clinical impression that it favored the onset of the attacks.

Patients with cor pulmonale seemed to be more prone to toxic manifestations. Old, emaciated patients presented evidence of toxicity earlier than younger patients in better nutritional conditions.

Digitalis glycosides proved to be safe in patients with a recent myocardial infarction and heart failure. There were good results and no complications. On the other hand, special care was taken, and the dose used was always smaller.

Cases with incomplete A-V block did not show greater complications than cases with normal rhythm.

There was definite correlation in most of the cases between the degree of reduction in size of the heart and clinical improvement. Hearts of normal size did not decrease following digitalization.

No close relationship was observed between diminution of venous pressure and decrease of circulation times.

The reduction in pulse in the control group was insignificant although the average rate before treatment did not differ from that of some digitalis groups.

Persons of the control group did not show evidence of toxicity. Normal hearts, therefore, are not more sensitive than sick hearts. Patients with more severe degree of failure developed signs of toxicity less frequently than cases with moderate failure.

Out of 12 ambulatory patients, five developed toxicity. The earliest sign of toxicity

was weakness, particularly in the ambulatory group. Loss of appetite was next.

Ventricular extrasystoles before treatment do not constitute a contraindication to the treatment. Usually, they disappeared after digitalization.

Hypertensive patients with renal insufficiency developed evidence of toxicity much earlier than others. Lesser elimination of digitalis might be the explanation. Therefore, such cases would need a smaller dose of digitalis for adequate treatment.

Rating of Drugs

Before attempting to formulate in terms of units the final results, it is useful to present the individual data based on each criterion of evaluation.

(1) *Reduction of Pulse at the End of Treatment:* The average value for all cases including both those with sinus rhythm and those with atrial fibrillation revealed that the greatest effect was obtained by cedilanid D and digoxin, the smallest by acetyl-digitoxin. The results are as follows:

(1)	Digoxin (alternative series)	30.6
(2)	Cedilanid D	27
(3)	Digitoxin	14
(4)	Ouabain	10
(5)	Gitalin	9
(6)	Acetyl-digitoxin	6

In considering this, it should be kept in mind that, out of 136 cases, 119 had sinus rhythm. Therefore, the above rating might not be valid for a large group with atrial fibrillation.

(2) *Rapidity of Improvement:* Based on the clinical onset of improvement, this was the greatest for ouabain, smallest for digoxin, as follows:

(1)	Ouabain	1st–2nd day
(2)	Digitoxin	2nd day
(3)	Cedilanid D	2nd–3rd day
(4)	Gitalin and digoxin	3rd day
(5)	Acetyl-digitoxin	3rd–4th day

(3) *Changes of Venous Pressure and Circulation Times:* On the basis of these data, two groups became apparent: digitoxin, acetyl-digitoxin, and digoxin were more effective while gitalin, cedilanid D, and ouabain were less effective. This indicated that the clinical evidence of improvement is not always paralleled by objective changes revealed by those two important methods. The results were as follows:

(a)	Digoxin Digitoxin Acetyl-digitoxin	70 units
(b)	Gitalin Cedilanid D Ouabain	50 units

(4) *Reduction in Size of the Heart:* As stated above, this reduction was measured in centimeters on the chest films. It was most marked for digitoxin and acetyl-digitoxin, least marked for cedilanid D. The data were as follows:

		cm
1	Digitoxin	3.2
	Acetyl-digitoxin	3.2
	Digoxin (larger dose)	3.0
2	Gitalin	1.5
3	Ouabain	0.8
4	Digoxin (smaller dose) Cedilanid D	0.7–0.4

(5) *Electrocardiographic Changes:* The rating of ECG changes, which we consider detrimental, was as follows:

		Units
(a)	Digitoxin	53
(b)	Digoxin (larger dose)	32
(c)	Gitalin	20
(d)	Ouabain	18
(e)	Acetyl-digitoxin	11
(f)	Digoxin (smaller dose)	8
(g)	Cedilanid D	6

(6) *Toxic Manifestations:* The toxic manifestations were greatest for digoxin, slightest for cedilanid D as follows:

		Units
(a)	Digoxin (larger dose)	64
(b)	Ouabain	50
(c)	Gitalin	35
(d)	Digitoxin Acetyl-digitoxin	15
(f)	Digoxin (smaller dose) Cedilanid D	3

(7) *Overall Rating:* Overall rating of the drugs including the ECG changes* (as negative

* In order not to duplicate certain ratings, changes of rhythm already counted in the ECG evaluation were not counted again as clinical data.

value) gave the first place to acetyl-digitoxin, the last to ouabain. The data are as follows:

		Units
(a)	Acetyl-digitoxin	90
	Digitoxin	80
(b)	Digoxin	54
	Cedilanid D	50
(c)	Gitalin	45
(d)	Ouabain	20

(8). *Overall Rating (ECG not considered)*:* As the negative value of severe ECG changes might be controversial, we have also made an overall rating without considering them. The data are then as follows:

		Units
(a)	Digitoxin	83
(b)	Acetyl-digitoxin	
(c)	Digoxin	69†
(d)	Cedilanid D	51
(e)	Gitalin	46
(f)	Ouabain	20

These ratings, even though incomplete and empirical, led to the following conclusions.

If reduction of the pulse is desired, digoxin or cedilanid D offers the best effect. If reduction of the heart size is desired or venous engorgement is severe, digitoxin or acetyl-digitoxin is to be preferred. In patients with rapid onset of toxic reactions, digoxin, cedilanid D, acetyl-digitoxin, and digitoxin are equal to each other but superior to others. If one wishes a rapid improvement, ouabain is still the best, but digitoxin follows immediately.

For intramuscular use, digitoxin was the only preparation which was well tolerated, as it was not too painful. The effect was similar to that of the same drug by intravenous injection.

On the basis of the overall rating, digitoxin would be preferred for a short range course; acetyl-digitoxin for a long range course (theoretically, less damaging effect on the myocardium). Digitoxin offers a somewhat greater chance of toxicity in ambulatory cases (greater accumulation); acetyl-digitoxin, a somewhat greater chance that the patient may not be adequately digitalized (greater rapidity of elimination). Digoxin, cedilanid D and gitalin are probably in an intermediate group.

* Disturbances of the rhythm were rated only as clinical manifestations (see Table of Rating).

† This figure was obtained by excluding patients who interrupted the treatment.

Discussion

THE PROBLEM OF DOSE

The first problem we had to cope with was that of dose. There are relatively few publications dealing with doses by the intravenous route and their data vary widely. On the other hand, as it was desirable to compare ouabain with the other drugs on an equal plan, it was imperative to prefer the intravenous (or intramuscular) to the oral route. The intravenous route, moreover, had the advantage of excluding possible causes of error due to improper absorption by the gastrointestinal tract and permitted a better comparison between digitoxin, more completely absorbed, and the lanata glycosides (Kwit, Gold, and Cattell).[10]

Our dosage was based on the daily doses indicated in Table III. It was initially considered that they would give a complete digitalization within two or three days and would maintain it until the end of the study. Actually, the conclusion of the present study was that the following should be considered average total doses for intravenous digitalization:

	mg
Digitoxin	1.2–1.4
Acetyl-digitoxin	1.4–1.6
Digoxin	2.0–2.2
Cedilanid D	2.0–2.2
Gitalin	4.0–5.0
Ouabain	0.50–0.75

On the basis of this, digitoxin, acetyl-digitoxin, and Gitaligin® were given in adequate doses. On the other hand, in the first series of cases, *lanoxin (digoxin) led to some degree of overdigitalization.* For this reason, a second series received smaller doses. On the other hand, *cedilanid and ouabain failed to reach the optimum level.* This statement is in contrast with published dosage indications which consider that the total average digitalizing dose with digoxin is 4 mg, with digitoxin 2.25 mg and with gitalin 6 mg (DeGraff *et al.*[4]). The difference is largely due to the fact that the above authors probably add the amounts administered each day until full digitalization is obtained. This

method is incorrect. We add the doses of each day, and we subtract the dose eliminated each day (average, based on animal experimentation) as percentage of the total received.* This method allows one to obtain a figure which is actually corresponding to that existing in the body. This may partly explain the greater toxicity found with digoxin. However, this drug actually had greater toxicity because, in some cases, treatment had to be interrupted before digitalization was complete.

Ouabain was found to be difficult to handle. The dose of 0.5 mg was too high for one single injection and was soon abandoned. The total dose of 0.5 mg in two injections was at times inadequate for a complete effect. It is likely that complete and safe digitalization would be obtained only with three daily injections of 0.25 mg at eight-hour intervals.

SPECIAL INDICATIONS OF THE VARIOUS GLYCOSIDES

Our separate ratings give certain indications:

(1) *For Severe Tachycardia:* The best glycosides are cedilanid D and digoxin. In this respect, our data are in contrast with previous findings (see Rothlin and Bircher[11]).

(2) *For Rapid Effect:* The best was ouabain followed by digitoxin. This should not cause surprise. Older studies compared intravenous ouabain with oral digitoxin. Ouabain is more rapid than digitoxin; its effect starts within three to five minutes (DeGraff *et al.*[4]) and is complete within two hours (Gold[7]). Digitoxin starts within 10 to 30 minutes (personal observation), and its effect is complete after about six hours.[7] The difference is not clinically significant in the great majority of cases. We found no difference between intravenous and intramuscular digitoxin. The latter route might be preferred by some, even though it might add 20 to 30 minutes to the onset of effect.

(3) *For Cases with Severe Hepatic Engorgement:* Digitoxin, acetyl-digitoxin, and digoxin are equally good, and superior to the others.

(4) *Heart Size*: A previous study of Luisada and Diamond on isolated papillary muscles had proven that ouabain is far more powerful than digitoxin in causing a diastolic shortening of the myocardial fibers. Acetyl-digitoxin even caused elongation of these fibers in concentrations similar to those obtained with clinical doses. The present study showed that digitoxin and acetyl-digitoxin were equally effective in reducing the cardiac size, and were superior to ouabain. This indicates that the overall effect of better systolic contractions and the decrease of residual blood are more important in determining diastolic length of the fibers than direct diastolic effect of the drug.

(5) *The Electrocardiographic Changes:* Varying degrees of S-T depression and lowering or inversion of T can be observed for any drug. However, they were much greater for digitoxin than for the others. Acetyl-digitoxin, cedilanid, and digoxin (reduced dose) obtained the greatest clinical improvement with the minimal ECG change. This should lead to two conclusions:

(a) There is no proportion between clinical digitalization and ECG changes; (b) in patients with severe ECG changes due to myocardial damage (including severe ventricular strain), acetyl-digitoxin or digoxin should be preferred to digitoxin. This is based on the observation that long-lasting digitalization with digitoxin causes degenerative changes of the myocardium (Bauer,[2] Hu *et al.*[9] Büchner[3]) while that with cedilanid is not followed by similar changes (Fahr and La Due).[5]

(6) *Toxicity:* The minimal toxicity was found for cedilanid followed by acetyl-digitoxin and digitoxin. Any of the three above drugs should be preferred to the other glycosides in cases with a low threshold of toxicity. If severe toxic manifestations are feared, then cedilanid should be preferred.

(7) *Overall Rating:* The overall rating has obviously a limited value, as indicated by the above considerations. Still, it is interesting to

* The daily ratio of dissipation for intravenous doses, studied by Rothlin and Bircher, is as follows:

	Per cent
Strophosid (and probably ouabain)	50
Cedilanid D (and probably digoxin)	20
Digilanid (and probably gitalin)	20-25
Acetyl-digitoxin	14
Digitoxin	7

(The notes in parentheses are our own.)

note that, if no attention is paid to the ECG, digitoxin and acetyl-digitoxin are first. If the ECG changes are considered as having a negative value (the authors favor this consideration), then acetyl-digitoxin reaches the first position. It is obvious that other considerations may prevail. For example, digitoxin was the only drug that could be given by the intramuscular route without causing excessive pain. Digitoxin, having a lower rate of elimination, will give a more constant level of digitalization. On the other hand, even though less toxic in a short term treatment, digitoxin may be more damaging to the myocardium in a long term treatment (ECG changes, frequent clinical observation of arrhythmias, etc.) and digoxin or cedilanid might be preferred.

Gitalin occupied in all ratings an intermediate position. It should be considered as equivalent to a complete extract of digitalis, with all its advantages and disadvantages.

Summary

A study was made in order to investigate if any clinical difference could be found between the effects of several digitalis and digitalis-like preparations.

The drugs used were *digitaline* (digitoxin), *acylanid* (acetyl-digitoxin), *lanoxin* (digoxin), *cedilanid D* (deacetylated-lanatoside C), *gitaligin* (gitalin), and *ouabain*.

These drugs were administered to 162 cases (138 suffering from heart failure and 24 controls) by intravenous injections (intramuscular in some). Full digitalization was obtained within two to four days with comparable doses. Clinical data, venous pressure and circulation times, roentgenologic and electrocardiographic data, were noted for seven days.

A method of rating the effect of the drugs in the individual cases is described.

The dose which is effective for intravenous digitalization is described for each drug on the basis of the present study. This total dose was ascertained by subtracting the average daily eliminated dose from the total received.

The greatest effect on heart rate was obtained with digoxin and cedilanid.

The greatest rapidity of effect was obtained with ouabain followed by digitoxin.

The greatest decrease of signs of congestion was obtained with digitoxin, acetyl-digitoxin or digoxin.

The greatest decrease of cardiac size was obtained with digitoxin or acetyl-digitoxin. This does not confirm previous studies of the authors according to which ouabain would exert a greater action than the above glycosides.

The greatest changes of the electrocardiogram were exerted by digitoxin; the smallest, by cedilanid. This was considered as a point in favor of the latter.

The greatest toxicity was found with digoxin while digitoxin did not seem to present special problems.

Gitalin seems to have an intermediate position from the various points of view.

The overall rating of the glycosides is discussed. This, however, should not be unduly stressed, as special indications were found for several glycosides.

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Clinical Evaluation of Acetyl-Digitoxin*

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DIGITALIS therapy of heart failure and the arrhythmias has been greatly extended and made more precise with the advent of the cardiac glycosides. Differences exist in clinical effect from one glycoside to another and may be due to variations in degree of absorption, serum binding power, toxic cumulation and dissipation. Also, it is well-known that the individual response to digitalis is quite variable, suggesting that experimentation is highly desirable to find the right glycoside which will be most beneficial to any given patient. However, most physicians prefer to limit the number of drugs in any one category and are ever on the lookout for a single drug which will serve the greatest number of patients. In a search for a glycoside having a broad range of application, Stoll and Kreis[1] isolated Acylanid® from digitalis lanata by subjecting lanatoside A to enzyme hydrolysis. Acylanid is acetyl-digitoxin, differing from digitoxin through the presence of an acetyl radical attached to the third digitoxose in the molecule. Pharmacologic study by Rothlin, Bircher, and Schalch[2] has demonstrated acetyl-digitoxin to be strongly bradycardic, well-absorbed, and less toxic than digitoxin.

They found acetyl-digitoxin to be a well-defined, pure cardiac glycoside free of biologic assay variations in contrast to digitoxin, which, though chemically well-defined, did not show uniform activity when batches from different sources were analyzed. It was found that absorption of acetyl-digitoxin from the gastrointestinal tract comes close to that of digitoxin and that its duration of action is somewhat shorter than that of digitoxin. Overdosage of acetyl-digitoxin in chronic cat experiments induced less frequent emesis, fewer irregularities, and fewer histologic changes in the heart muscle and conductive system. Better toleration, more rapid dissipation, and a lesser degree of cumulation pointed to a reduced toxicity.

The clinical efficacy of acetyl-digitoxin has been revealed in a number of studies which have shown it to be very well-tolerated and useful for both digitalization and maintenance.[3–9] Maher and Pullen,[3] Brill, Burgner, and David,[4] and Crouch, Hejtmancik, and Herrmann,[5] have noted especially and favorably that anorexia, nausea, or vomiting usually appeared as the first symptoms of overdosage, and they consider this a highly desirable warning to prevent the development of the more serious toxic arrhythmias. Also noted[5] was the spread between dissipation of toxic effects within 24 to 72 hours and evidence of therapeutic effect for periods up to 17 days after discontinuation of the drug.

This report details our experiences with acetyl-digitoxin in 35 patients over a period of ten months.

METHODS AND MATERIALS

Thirty-two patients were digitalized with acetyl-digitoxin and maintained on this glycoside for variable periods of observation. All of these patients were hospitalized, and had never been on a digitalis preparation before or had not taken any digitalis preparation for a period of at least three weeks prior to administration of acetyl-digitoxin.

Administration of acetyl-digitoxin was preceded by the following determinations in each patient: venous pressure, circulation time with decholin and ether, chest roentgenogram (and fluoroscopy in some cases), vital capacity, electrocardiogram, and routine laboratory studies. All patients were placed on bed rest and

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a diet with no more than 2.0 g NaCl daily. Diuretics were withheld wherever possible during and following digitalization in order to better evaluate diuresis due to the above measures and the drug. Antihypertensive and other cardiovascular drugs were given as indicated.

Acetyl-digitoxin was usually employed in doses of either 0.2 mg every four hours or 0.4 mg every six hours depending on the urgency of the need for digitalization. The ventricular rate governed this in cases of auricular fibrillation. Several patients with auricular fibrillation received single doses of 1.4 to 1.6 mg in order to determine the time of onset of effect and time of maximal effect. In most of the cases of sinus rhythm we chose to give the drugs until significant diuresis occurred or until early toxicity was noted so as to determine the nature of the toxic effects and also to be assured of adequate digitalization. Patients with auricular fibrillation were given the drug until the ventricular rate was decreased to 60 to 75 per minute and did not increase more than 10 per cent after exercise.

All patients were observed at least once daily in reference to this study and the following were recorded daily: functional class (New York Heart Association classification), body weight, blood pressure, apical and radial rates, heart rhythm, respiratory rate, heart size, edema, dyspnea, pulmonary rales, liver size and tenderness, signs of toxicity, and dosage of acetyl-digitoxin. Electrocardiograms were repeated frequently. In many cases vital capacity, venous pressure, circulation times, and chest roentgenograms were repeated serially during the observation period.

Tables I and II show the age ranges for the group and the type of heart disease. It can be seen that there was a rather even distribution of patients in the 5th, 6th, 7th and 8th decades of life. Arteriosclerotic heart disease was the type of heart disease diagnosed in the majority of cases. There were eight male and 24 female patients in this group; as the patients were selected for this study only on the basis of the presence of indications for digitalization, the reason for the preponderance of females is not obvious.

Nineteen of the patients had sinus mechanisms prior to digitalization: five of these had frequent supraventricular premature contractions. Seven patients had auricular fibrillation, one had paroxysmal auricular tachycardia, one had auricular tachycardia with a 2 : 1 atrioventricular block, two had sinus bradycardia, and one had a wandering pacemaker.

Of the 32 patients digitalized with acetyl-digitoxin, it was possible to follow 13 for periods of from several weeks to six months on maintenance doses of acetyl-digitoxin. In addition to these, there were three other patients who had been maintained previously on other cardiac glycosides who were changed to maintenance doses of acetyl-digitoxin and followed for similar periods of time. All patients were initially placed on 0.2 mg maintenance daily doses; dosage was adjusted as indicated by effect on heart rate, body weight, signs of congestion, toxic effects, etc.

Results

Acetyl-digitoxin proved to be quite effective

TABLE I

Ages of Patients Digitalized with Acetyl-digitoxin

Age	Number
40–50	6
50–60	7
60–70	9
70–80	9
80–90	1
Total	32

TABLE II

Type of Heart Disease in Patients Digitalized with Acetyl-digitoxin

Type	Number
Arteriosclerotic	18
Cor pulmonale	6
Hypertensive	3
Thyrotoxic	1
Fibrous pericarditis	1
Rheumatic	1
Syphilitic	1
Tumor (?)	1
Total	32

in this group of patients. In only four patients was congestive heart failure not improved by digitalization; two of these had previously shown no improvement when treated with digitoxin; one of these died and was found at autopsy to have had a pulmonary embolus; the remaining two patients in whom no improvement occurred with acetyl-digitoxin died during hospitalization and were discovered at autopsy to have had a fibrous pericarditis and a severe bronchopneumonia, respectively, in addition to signs of heart failure.

Two patients with auricular fibrillation converted to a sinus mechanism after receiving acetyl-digitoxin. Paroxysmal auricular fibrillation in one patient was converted to a sinus mechanism within six hours after the administration of 1.2 mg acetyl-digitoxin. A patient suspected to have metastatic carcinoma involving the heart had been having frequent episodes of paroxysmal auricular tachycardia, occurring as often as two or three times daily; after being digitalized with acetyl-digitoxin, she has not had a recurrence of the tachycardia in a two month period of observation. Auricular tachycardia with a 2 : 1 atrioventricular block changed to a sinus rhythm in another patient after acetyl-digitoxin.

SPEED OF ONSET OF ACTION

To determine how soon cardiac effects occurred after ingestion of acetyl-digitoxin three patients with atrial fibrillation were given single oral doses of 1.4 or 1.6 mg of the drug. Apical rates were recorded at least hourly until maximal effect was attained; the electrocardiogram was repeated at two-hour intervals in two cases.

Using a 10 per cent reduction in ventricular rate as the criterion, it can be seen from Figure 1 that acetyl-digitoxin had an onset of observable cardiac effect within two to four hours after oral administration. Electrocardiographic changes (ST-T wave) attributable to digitalis were observed within four to six hours after a single oral dose in these patients (Fig. 2). Maximal effect in these cases as determined by lack of further reduction in ventricular rate occurred at 8 to 16 hours after oral administration of the drug.

DIGITALIZING DOSE

In all cases where digitalization was accomplished over a period of time longer than one day, a daily dissipation and excretion factor of 0.2 mg of acetyl-digitoxin was subtracted from the total dosage administered during this period in computing the digitalizing dose. Also, whenever toxicity was produced during digitalization, the last dose (0.2 or 0.4 mg) was subtracted from the total.

The digitalizing dose in this group ranged from 1.0 mg to 4.0 mg when calculated on a 24-hour basis as described above. (Fig. 3). It can be seen that the great majority

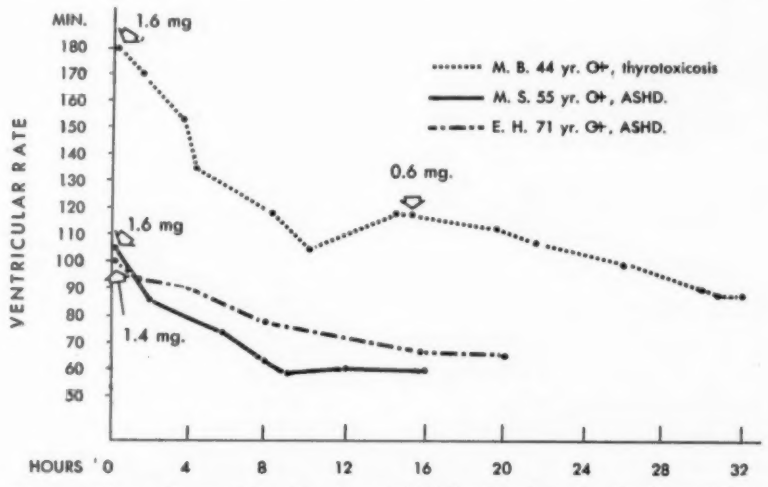

Fig. 1. Time of onset of action of acetyl-digitoxin given in single oral dose to three patients with auricular fibrillation.

required from 1.0 to 2.0 mg for digitalization, with well over 50 per cent of the cases falling between 1.4 mg and 2.0 mg. The group requiring the smaller dosages (1.0–1.2 mg),

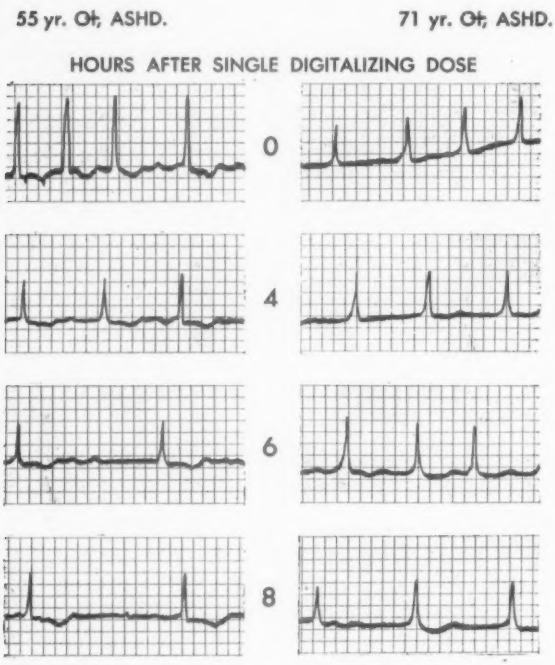

Fig. 2. Time for electrocardiographic evidence of digitalis effect (ST-T wave) after single oral dose of acetyl-digitoxin in two patients with auricular fibrillation.

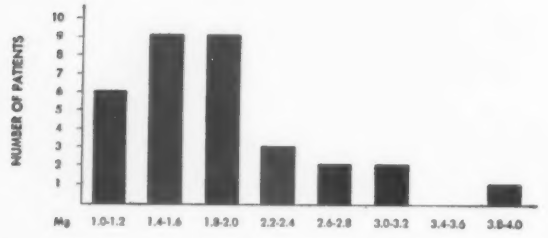

Fig. 3. Digitalizing doses of acetyl-digitoxin in 32 patients, calculated on a 24-hour period of digitalization.

usually had a sinus bradycardia or a slow ventricular rate. The patient who received the largest dose, 4.0 mg, had severe cor pulmonale secondary to bronchiectasis and died with a pulmonary infarction several days after admission. Only seven other patients required more than 2.0 mg; of these, one had moderately severe thyrotoxicosis, two had cor pulmonale, and three had very severe arteriosclerotic heart disease.

TOXIC EFFECTS

Thirteen patients developed toxic effects while being digitalized. It should be re-emphasized, however, that most of these occurred because the plan of study was to give the drug until early toxicity was produced when the end-point for digitalization was not clear-cut. There were, in addition, eleven patients who developed toxic reactions while maintenance dosage was being adjusted.

Table III summarizes the nature of the toxic

TABLE III

Toxic Effects Observed or Induced in 24 of 35 Patients Receiving Acetyl-Digitoxin

Symptoms or signs	Number
Gastrointestinal only	
Anorexia, nausea, and/or vomiting	15
Diarrhea	2
Cardiovascular only	
Auricular tachycardia	1
Auricular fibrillation	2
Sinus bradycardia	1
Ocular	1
Toxic psychosis (suspected relationship only)	1
Cardiovascular and gastrointestinal	
Anorexia, later sinus tachycardia with varying degree A-V block	
Later auricular fibrillation with VPC's.	1
Total	24

effects. It can be seen that the great majority had gastrointestinal symptoms only. Cardiac abnormalities alone were possibly caused by acetyl-digitoxin in four cases; in one, an episode of auricular tachycardia occurred, but was terminated without recurrence five minutes after sedation and intravenous Vasoxyl®; a sinus bradycardia (rate 40–50) occurred in one and auricular fibrillation in two others while on the drug. In one case cardiac abnormalities occurred after the onset of gastrointestinal complaints. Four of the five patients who developed cardiac abnormalities received

2.0 mg or more of acetyl-digitoxin as the digitalizing dose. One patient developed a toxic psychosis while on acetyl-digitoxin; however, the presence of a simultaneous stormy postoperative course would not allow definite implication of this drug as the causative factor.

The toxic manifestations lasted one day or less after discontinuation of the drug in over half of the cases. In only three instances did they last longer than three days; gastrointestinal complaints persisted for four days in one and five days in another of these; sinus bradycardia persisted about eight days in one case.

MAINTENANCE DOSE

Of the 16 patients on a maintenance regimen of acetyl-digitoxin for periods ranging from several weeks to six months, eleven were well-maintained on 0.2 mg daily. In four patients, this dose caused toxic symptoms and was obviously too high since all were subsequently well-maintained on 0.1 mg daily. One patient was satisfactorily maintained on 0.3 mg daily.

Discussion

This study has shown acetyl-digitoxin to be an effective and well-tolerated cardiac glycoside in the treatment of congestive heart failure and arrhythmias occurring in various types of heart disease. Diuresis, diminution of heart size, reduced venous pressure, decreased circulation time, and loss of edema fluid revealed the usefulness of acetyl-digitoxin in relieving congestive heart failure. The slowing of the ventricular rate in auricular fibrillation and the number of patients with rapid supraventricular tachycardia who reverted to sinus mechanisms after digitalization with this agent also attest to its effectiveness.

In the patients we have studied, the digitalizing dose varied from 1.0 to 4.0 mg over a period of 24 hours with the majority requiring between 1.4 and 2.0 mg. This is in close agreement with the results obtained by Crouch, Hejtmancik, and Herrmann,[5] Doherty,[8] Brill, Burgner, and David,[4] and Maher and Pullen.[3] Goldfarb, Thorner, and Griffith[6] used somewhat larger doses as did Zilli and Luisada[9] who found it necessary to give 2.4 mg to 3.6 mg over a period of 2 to 4 days; if one allows a daily dissipation and excretion factor of 0.2 mg per day to be subtracted from these higher doses, it can be seen that the difference in digitalizing doses in their cases is not as great as it seems at first. Allowing for the above dissipation and excretion factor, most of the patients studied by Loeffler, Essellier, and Forster[7] required between 2.4 mg and 5.6 mg for initial digitalization. In spite of the known individual variation in requirements and toleration to digitalis, we are unable, at the present time, to reconcile our data with those of Loeffler and his associates.

Most of our patients were well maintained on a dose of 0.1–0.2 mg of acetyl-digitoxin per day. One patient required 0.3 mg per day. These results are in agreement with those of most other investigators but lower than the 0.2 to 0.3 mg, and occasionally up to 0.6 mg maintenance dose employed by Loeffler and his associates.[7]

Well over one-half of our patients developed toxicity while on acetyl-digitoxin, but in most of the cases, this was deliberately produced. The fact that most experienced only gastrointestinal symptoms is of great importance. Cardiac abnormalities which might possibly be due to digitalis intoxication occurred in only four of these cases prior to the appearance of gastrointestinal symptoms. As termed by Crouch and his associates[5] and noted by others[3,4] these gastrointestinal symptoms "act as a desirable safety valve measure," a useful property resembling that obtained with digitalis leaf. In almost every case where toxicity was produced, the manifestations disappeared within 1 to 3 days, a rapid loss of toxicity which has also been noted with favor by Crouch and his associates[5] and by Brill, Burgner, and David.[4]

Summary and Conclusions

(1) Thirty-two patients were digitalized orally with acetyl-digitoxin, the digitalizing dose ranging from 1.0 mg to 4.0 mg with the majority requiring between 1.4 mg and 2.0 mg when calculated on a 24-hour period of digitalization.

(2) The maintenance dose of acetyl-digitoxin ranged from 0.1 mg to 0.2 mg per day.

(3) Acetyl-digitoxin was found to be an effective, quick-acting, and well-tolerated cardiac glycoside, and a useful addition to the therapy of heart failure.

(4) Toxicity was deliberately produced in most of the patients. It was observed that the initial manifestations of toxicity were usually gastrointestinal and that these subsided within three days after discontinuance of the drug in almost every case.

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Clinical Evaluation of Intramuscular Digitoxin in the Management of Congestive Heart Failure*

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IT IS NOT uncommon for a situation to arise wherein the intramuscular administration of digitoxin is decidedly preferable to either the oral or intravenous route. The oral route is precluded in the presence of nausea, vomiting, coma, lack of patient cooperation and gastrointestinal pathology or surgery. Furthermore, hepatic engorgement, which frequently accompanies congestive heart failure, can seriously interfere with absorption of the drug. The intravenous route, on the other hand, may be hazardous and often presents difficulties in administration. With an obese or edematous patient an intravenous injection becomes troublesome because of the difficulty attendant upon locating the vein. Indeed, the intravenous route is the one of choice only in instances where a very rapid effect is necessary,[1,2] and in such cases lanatoside C, rather than digitoxin, is preferable.

Intramuscular administration of digitoxin is the preferred alternative when the oral route is precluded. For want of a more suitable preparation, alcoholic solutions of digitalis glycosides intended for intravenous administration have been injected intramuscularly. However, the high alcoholic content of these solutions, approximately 40 per cent, causes the patient considerable pain and may possibly result in tissue slough.

Recently Strauss *et al.*[3] have reported the highly satisfactory response of 21 congestive heart failure patients to treatment with a digitoxin solution specifically designed for intramuscular use. In this solution digitaline nativelle (0.2 mg per cc) is dissolved in a vehicle consisting of polyethylene glycol 300 (28.6 per cent), glycerine (43.8 per cent), benzyl alcohol (4.0 per cent), ethyl alcohol (5.0 per cent) and water. The solvent materials, in combination and individually, have been found free of toxic or irritating effects when injected intramuscularly.[3,4,5]

Inasmuch as an effective intramuscular digitoxin can satisfy a real need in the management of congestive heart failure, this study was undertaken to evaluate the preparation clinically.

MATERIAL AND METHOD

Thirty-six patients with mild to moderate congestive heart failure were chosen at random from the medical service of a large municipal hospital. Six of the group were rheumatic, nine were hypertensive, and twenty-one were diagnosed as hypertensive arteriosclerotic heart disease. The group included 29 males and 7 females ranging in age from 29 to 83 years.

The criteria for the various diagnoses are described below:

Rheumatic Group: A history of rheumatic fever coupled with evidence of valvular disease as revealed by auscultatory findings and/or characteristic fluoroscopic configurations.

Hypertensive Group: Fixed systolic blood pressure levels above 170 and diastolic levels above 110, with fluoroscopic evidence of left ventricular outflow tract enlargement.

Arteriosclerotic Group: Historical or electrocardiographic evidence of the anginal syndrome,

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coronary insufficiency, prior myocardial infarction with or without evidence of conduction disturbance in the absence of medication.

Of the entire group, 23 patients were admitted with auricular fibrillation; 13 had a sinus mechanism, and 6 had never received any digitalizing preparation prior to admission.

All medications other than barbiturate, and in some instances morphine sulfate, were withheld for a period of two weeks prior to the commencement of the study. Venous pressures were determined, and chest x-rays, fluoroscopy and electrocardiograms were done. Heart rate and liver size were recorded, and direct ballistocardiography was performed on those patients with a sinus rhythm.

To initiate digitoxin therapy, a solution* containing 0.6 mg was injected—0.3 mg in each buttock. At the end of four hours, the patient was reassessed. As required, doses of 0.2 mg of digitoxin were given at four-hour intervals until an end point was established, as determined by the criteria described below:

For the Fibrillating Group: Abolition of the pulse deficit following exercise. Reversal of signs and symptoms of decompensation. Electrocardiographic signs of intoxication.

For the Non-Fibrillating Group: Appearance of ST segment depression and inversion of the T waves on the electrocardiogram, or the appearance of electrocardiographic evidence of intoxication; significant decrease in pulse rate and venous pressures; decrease in liver size and absence of symptoms of congestive failure; ballistocardiographic evidence of compensation included separation of H and J waves, increase in the amplitude of systolic complexes, deaccentuation of diastolic waves, decrease in respiratory variation and restitution of repetitive form.

Following digitalization, patients were maintained during the next 10 days by daily intramuscular injection of digitoxin. The drug was then discontinued and the patients were allowed to return to the decompensated state which was marked by increased heart rate and venous pressure, deterioration of the ballistocardiogram and recrudescence of the signs and symptoms of heart failure.

* Digitaline nativelle intramuscular.

Results

Without exception, a substantial reduction in pulse rate and venous pressure occurred within four hours following a single initial dose of intramuscular digitoxin. Prior to digitalization, ventricular rates ranged from 84 to 126, with an average rate of 102, while venous pressures ranged from 180 to 320 mm of water and averaged 224 mm. At the end of four hours, the range of ventricular rates was 64 to 112, average 82, and the venous pressures ranged from 120 to 210 mm with a mean of 168 mm. The digitalizing dose varied from 1.2 to 2.0 mg and averaged 1.4 mg.

After digitalization was complete, all patients were successfully maintained in the compensated state by an average daily dose of 0.2 mg (1 cc) of digitoxin intramuscularly. None of the patients exhibited any systemic signs of intoxication after receiving the drug, and electrocardiographic evidence of intoxication occurred in only three cases.

Parenteral mercurials were administered to 14 patients as an ancillary measure in controlling the decompensated state. This was followed by further decrease in venous pressure.

Thirty-three per cent of the patients experienced no discomfort following the initial digitalizing dose, which in no instance caused more than moderate muscle pain. The maintenance dose of 1 cc elicited complaints of slight pain from only one-half the group. Nodule or abscess formation was completely absent.

Upon discontinuance of the drug, the patients reverted to the decompensated state within two to nine days, the mean for all patients equalling five days.

Discussion

Intramuscular digitoxin efficiently controlled the signs and symptoms of congestive heart failure in all patients. The magnitude of decrease in ventricular rate and venous pressure which occurred during the first four hours following the initial dose was of the same order as that found for oral or intravenous administration of digitoxin by Gold[2] and Strauss[3]. The weight for weight equivalence of cardiotonic action between the intramuscular and oral dosage forms demonstrated by the latter investigator is of par-

ticular advantage during maintenance therapy inasmuch as it is possible to simply interchange the two forms on an equiweight basis.

The ease of maintenance with intramuscular digitoxin noted during this study can be attributed to a slow, uniform excretory rate which was evidenced by the average of five days required for decompensation to recur after cessation of drug administration.

Pain following intramuscular injection of the preparation was of minor consequence. The mild to moderate discomfort which some of the patients experienced appeared to be in proportion to the volume injected and did not seem related to any irritating properties of the solution. The absence of any abscess or nodule formation indicates that the preparation is free of deleterious effect upon the tissues.

On the basis of this study, intramuscular digitoxin appears to be a non-irritating and effective agent for the management of cardiac arrhythmias and congestive heart failure. Particularly is this so when the speed and exigency of the intravenous route are unnecessary or not readily feasible, but parenteral therapy is nevertheless indicated by a physical or mental condition of the patient which precludes medication.

Summary

(1) Digitaline nativelle intramuscular, a digitoxin solution specifically designed for intramuscular injection, was clinically evaluated for the control of cardiac arrhythmias and congestive heart failure in a series of 36 patients.

(2) The signs and symptoms of congestive heart failure were efficiently controlled in all cases.

(3) The magnitude of decrease in ventricular rate and venous pressure which followed a digitalizing dose of intramuscular digitoxin was of the same order as is accomplished by oral or intravenous digitoxin.

(4) Maintenance of patients in the compensated state was readily attained with an average daily 1 cc. (0.2 mg) dose of intramuscular digitoxin.

(5) Pain following intramuscular injection of the preparation was of minor consequence. There were no undesirable local or systemic effects and the solution appears to be a safe and effective preparation.

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Experimental Studies

Force, Work, and Power Ballistocardiography*

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Introduction

Although ballistocardiographic records have been obtained for approximately 75 years, there is still a need for a useful method for analysis. Rather consistent configurational changes have been noted in certain cardiovascular diseases. Nevertheless, exceptions to these patterns occur often enough to limit the ballistocardiograph as a diagnostic instrument for a specific disease state. The most frequently used approach has been the arbitrary grading of the trace as to the degree of abnormality noted primarily during the respiratory cycle.[1] (This has been applied in the past only to traces obtained from the high frequency systems.) This type of approach is empiric and its clinical value depends chiefly upon the experience of the physician interpreting the traces. In addition, it is difficult to achieve standardization in different laboratories, and therefore this approach appears to be limited in usefulness.

Studies concerning the genesis of the ballistocardiogram similarly have been meager up to the present time, primarily because of the lack of suitable technics for animal investigations. The classic work of Starr and associates[2] has adequately demonstrated the importance of recoil and impact of blood (blood flow) in the genesis of the ballistocardiographic waves. However, their quantitative relationship to the normal and abnormal ballistocardiogram still appears to be unsettled, and more recent experimental work on the dog has demonstrated that there are forces, in addition to those associated with blood flow, produced by myocardial factors alone that are operative throughout the entire ballistocardiogram.[3] Physiologic correlations of the waves have shown that certain segments and points can be related, at least in part, to known physiologic events, such as right and left ventricular ejection.[4,5] However, instances are encountered in disease states which bear little or no relationship to known events and have forms which differ appreciably from the normal ballistocardiogram. Also, many waves in the abnormal trace are difficult to identify or label and new waves often appear to be present. Thus, the lack of uniformity in the interpretation of the ballistocardiogram has seriously limited its over-all clinical value and a method of analysis is needed. It appears reasonable to assume, from physical considerations and the apparent lack of specificity in disease, that the potential usefulness of the ballistocardiogram will be primarily in evaluating myocardial function and possibly reserve, and not as a diagnostic instrument. This, in itself, may be of no little importance as at the present time there are no methods readily

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available to estimate heart performance other than by the history of how much work or effort the patient is able to perform. If these traces offer a means by which various cardiovascular functions can be estimated, then the technic would have a very useful place in clinical medicine.

The purpose of this paper is to present several new approaches for ballistocardiographic analysis based primarily on physical principles. Like any new approach, the true value of these measurements remains to be established; however, studies in this laboratory prove most encouraging.[6] These methods apply only to the curves obtained from ultra-low frequency systems which have a linear response and register "pure" function of motion (displacement, velocity, or acceleration).[7]

Methods of Analysis of BCG

Recent studies in this laboratory emphasized the concept that the ballistocardiogram can be regarded as a complex waveform.[3] This hypothesis was based upon studies in the dog which indicated that both myocardial and blood flow forces are concomitantly taking place and summating; therefore, no segment of the waveform is due to a monogenetic force. If one assumes that this proposed concept for the genesis of the ballistocardiogram is true, then there are several methods of analysis which are applicable.

I. *Force of the Heart Beat:* The motion of the body in an ultra-low frequency system can be registered graphically as acceleration, and from the standard formula of mass (M) multiplied by acceleration (a)

$$F = Ma \qquad (1)$$

the theoretic force (F) associated with each heart beat can be calculated. This has been well described previously, and at the present time is one of the most frequently recorded traces.[7] The amplitude changes from the isoelectric line represent the headward or footward accelerations of the body, and if the system is properly calibrated, these figures can be substituted in the above formula (1) to obtain the forces in dynes. At the present time, only amplitude measurements of acceleration, and consequently peak forces of a given wave have been used. However, there are both practical and theoretic limitations to this type of analysis, and a given amplitude or force may depend in a great part on whether the many forces producing the waves are synchronous or asynchronous.[3] If two forces occur simultaneously, then the net amplitude will represent their summation, while if the same two forces are somewhat asynchronous, the absolute force as determined only by amplitude measurement will appear to be decreased. This suggests additional methods of analysis other than measurements of peak forces are needed to fully evaluate the force ballistocardiogram.

The area under an acceleration curve represents the first integral or velocity; however, if the area (A) under a given wave is divided by its distance or duration (d), the resultant represents the average acceleration.

$$\text{Average Acceleration } (\bar{a}) = \frac{A}{d} \qquad (2)$$

As duration as well as amplitude is considered in the above formula, the calculations should augment those obtained for peak amplitude alone. This can be used similarly, as in formula (1), to estimate average force.

II. *Impulse:* Impulse can be determined by measuring the area under the acceleration trace and multiplying this by the mass. Also it can be determined by measuring the average force* ($\bar{F}$) of a given wave and multiplying it by the time (t) or duration of the wave.

$$\text{Impulse } (I) = \bar{F} \cdot t \qquad (3)$$

III. *The Determination of Work and Kinetic Energy:* When body motion is recorded as acceleration, velocity, and displacement, there are many other possible calculations that can be performed which are based upon standard physical laws. The formula for the calculation of "work" (W) is force acting through distance (s).

$$W = Fs \qquad (4)$$

* It is important to distinguish between acceleration and force. Force represents the product of mass and acceleration, and the acceleration ballistocardiogram is not a force trace until it is converted by use of the appropriate formula.

This can be obtained from simultaneously recorded displacement and acceleration ballistocardiograms by converting the acceleration ballistocardiogram to units of force and multiplying this by the known displacement at that moment. As displacement ballistocardiograms are somewhat difficult to obtain because of the wide shifts of the baseline associated with respiration, as well as the small periodic motions of the bed, the calculation of work can be obtained more conveniently by using the velocity trace. Velocity records are reproducible and easy to obtain. In addition, stabilization of the baseline is not the problem as in displacement records, especially during held respiration. Only one function of motion is necessary for the calculation of work. If the velocity is calibrated, substitutions in the formula one-half the mass (M) times the velocity (v) squared represents the work.

$$\text{Work (W)} = \frac{Mv^2}{2} \qquad (5)$$

There are certain basic considerations which must be considered in using this formula. The amplitude from the isoelectric line in a calibrated system represents the body motion in terms of true velocity and thus any point on the entire ballistocardiographic curve can be substituted in formula (5) to obtain the instantaneous kinetic energy at that point. From a fundamental standpoint, kinetic energy and work are different in that work primarily represents a change in kinetic energy. However, since the velocity is zero at the onset of each wave, the instantaneous kinetic energy at a point on the velocity ballistocardiogram represents the accumulated work at that point. Thus, if one selects the maximum amplitude of any given wave as the velocity to be substituted in the above formula (5), such as the maximum amplitude of the I or J wave, the resultant represents change in the kinetic energy from the isoelectric line, or from zero velocity, and therefore indicates the accumulated work during the downstroke of the I wave, or the upstroke of the J wave. Theoretically, the work on the descending limb of the J wave, or the ascending limb of the I wave, would be equal to the initial accumulated work and the total work during the I wave, or the J wave, would be represented by twice that obtained using formula (5). Thus work can be calculated for any and all waves of the ballistocardiogram without regard to their etiology or configuration. This type of analysis becomes somewhat more difficult if there are major notches or directional changes in a given wave. A more accurate analysis then could be obtained by assuming that each projection is a separate wave in itself. However, for practical purposes the error is negligible in using the maximum amplitude to represent the accumulative work in the upstroke, even in traces in which several notches or footward changes in direction occur.

Theoretic consideration of the mechanisms during the descending limb of the J wave, or after peak velocity is reached, suggests that the descending limb represents active work, as the ultra-low frequency systems would not automatically return to the isoelectric line unless a counter force is applied. In addition, the descending limb of the J wave occurs during ejection, and therefore it can be assumed, from a physiologic standpoint, that there is active work taking place, although diminishing, during this portion of the cardiac cycle.

Average kinetic energy can be approximated from the average velocity (V), which in turn can be determined by measuring the area under a given wave (A) and dividing this by the distance (d)* of the wave.

$$\text{Average Velocity (V)} = \frac{A}{d} \qquad (6)$$

This can then be substituted in formula (5) to give the following formula:

$$\text{Average kinetic energy (KE)} = \frac{MA^2}{2t^2} \qquad (7)$$

This approach is not theoretically as sound as that obtained by using the instantaneous amplitude or velocity. The total kinetic energy in a wave could more accurately be obtained by adding all of the values for work, as determined from instantaneous velocity, and di-

* In a calibrated trace, distance (d) can be converted to time (t) by measuring the time required for the paper to move a given distance.

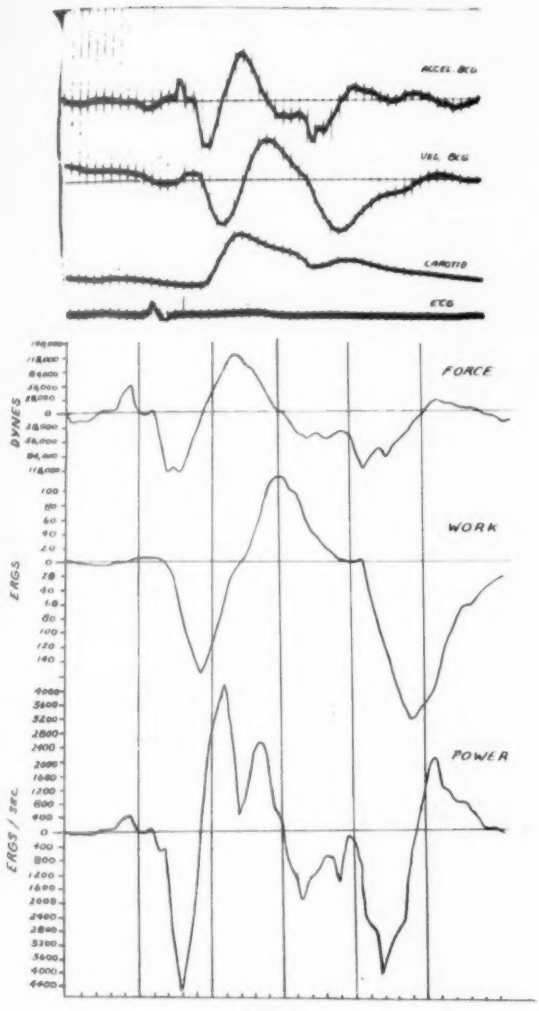

Fig. 1

Fig. 1. This presents the acceleration and velocity ballistocardiograms as well as the carotid pulse and electrocardiogram on a normal subject. Below are the derived curves for the force, work, and power functions. The vertical lines in the recorded ballistocardiograms represent 0.02 sec and the time marks on the lower part of the figure similarly indicate 0.02 sec. The force, work, and power traces are constructed from the onset of the QRS complex in the electrocardiogram. In the acceleration trace the calibration was such that a centimeter deflection represents an acceleration of 0.92 cm/sec squared. On the velocity tracing one centimeter deflection represents a velocity of 0.04 cm/sec.

To construct the *force trace* in the lower figure the absolute acceleration was determined for every 0.01 sec in the curve and this multiplied by the mass of the patient in grams in order to determine the force. The *work curve* was constructed from the velocity trace by determining the absolute velocity every 0.04 sec which was squared and then multiplied by one-half the mass of the patient in grams. In this way a point in the work curve was determined every 0.01 sec. The *power trace* was constructed by determining the force every 0.01 sec and multiplying this by the velocity at the same instance as determined by the simultaneous velocity trace. Both the work and power curves are given vectoral representation although actually they are not vectoral quantities. This was done merely for graphic purposes to indicate when work and power occurred in the footward direction. The subsequent figures of work and power curves were constructed in the same manner as those presented in this figure.

viding this by duration, or time, of the wave. As this is impractical, calculations using formula (7) appear to be useful in obtaining an estimation of the average kinetic energy. It introduces the unit of time, or distance, and therefore may augment the calculations of work. Obviously, total work during the entire cycle can be obtained by adding the values obtained for each wave and in addition, work per minute can be estimated by considering the heart rate.

IV. *Calculation of Power:* There are several possible approaches in determining power. Since power is work per unit of time, instantaneous power at any point in the ballistocardiographic complex can easily be obtained by multiplying the force at any point (as determined for the acceleration curve) by the simultaneously recorded velocity.

$$\text{Power (P)} = Fv \tag{8}$$

Since the work obtained using formula (5) represents the accumulated work in a given upstroke, such as the J wave, power also can be calculated by dividing it by time from the point where the curve intersects the isoelectric line to the point where the peak velocity is reached.

$$\text{Power (P)} = \frac{Mv^2}{2t} \tag{9}$$

Since twice the work obtained using formula (5) represents the accumulated work during a ballistocardiographic wave, the power associated with the total work of a given wave similarly can be obtained by multiplying the mass times the peak velocity squared and divided by the total duration of the wave.

$$\text{Power (of an entire wave)} = \frac{Mv^2}{t} \tag{10}$$

An additional method for estimating power can be employed using average kinetic energy

(formula 7). In this instance, the kinetic energy is divided again by the time or the duration of a given wave.

$$\text{Average Power} = \frac{MA^2}{2t^3} \qquad (11)$$

Technic

Ultra-low frequency ballistocardiograms were recorded on a bed suspension, previously described.[4] The bed suspension used has a natural frequency of 0.3 cycle per sec with no damping, and therefore functions essentially as an aperiodic system. Acceleration was sensed by a mercury sulfuric acid capillary accelerometer.[8] Velocity was obtained in two ways: (1) A specially constructed Smith-Perls bar magnet was obtained from the Bowen Company which had no filter circuit present and the output from the bar magnet and coil was fed directly into the recorder. With this type of pick-up, the frequency response was excellent and the signal was "pure" velocity. (2) The acceleration signal was integrated by an R-C integrator which has a frequency response from 1 to 30 cycles per sec. Both types of velocity traces were essentially identical in phase and configuration. The ballistocardiograms were recorded on a Scheiner Electronic Recorder.* With this instrument, traces were taken at paper speeds of 130 mm/sec so that accurate measurements could be made. Excellent amplification was obtained and the ballistocardiograms usually were above 4 cm in amplitude which aided in accurate measurements.

Results

From the considerations presented, it is possible to actually construct a work ballistocardiogram by taking the instantaneous velocities (every 0.01 sec) throughout the entire complex and substituting these in formula (5). The units of work can be expressed in grams, centimeters, seconds (ergs), and thus a curve can be plotted which represents the work throughout each point in the ballistocardiographic cycle. Figure 1 presents the acceleration and velocity ballistocardiogram from a normal subject and the force, work, and power traces to illustrate the methods used in deriving these curves.

Figure 2 represents the work curve from a normal subject, as well as from a patient with angina pectoris to illustrate the possible

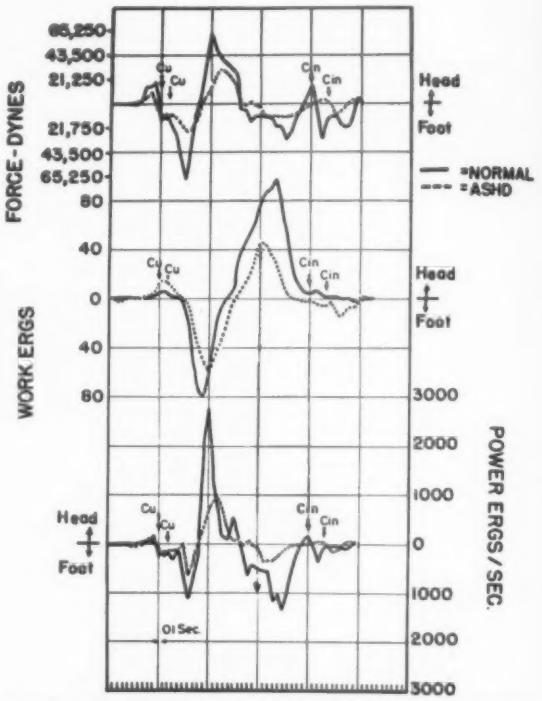

Fig. 2. This represents the force, work, and power ballistocardiogram constructed from the head-foot low frequency velocity and acceleration ballistocardiograms. The solid line represents the normal subject, while the dotted line represents a patient with arteriosclerotic heart disease (angina pectoris). The first CU represents upstroke in the carotid pulse in the normal subject, while the second represents the upstroke in the carotid pulse in the patient with arteriosclerotic heart disease (angina pectoris). CIN represents the incisural notches in the respective cases. The acceleration ballistocardiogram was converted into units of force as described in the paper. The patient with angina pectoris has a decrease in the over-all force ballistocardiogram. The normal work curve has two principal peaks, one in early systole and one in late systole. In this instance, it was represented as a vectoral quantity since the tracing was recorded in a head-foot axis although work units are actually scalar. Work during late systole in the patient with arteriosclerotic heart disease is reduced by half from that of the normal subject. The power curve is represented as the last tracing in the figure. Again note the marked decrease in the power in the patient with arteriosclerotic heart disease. From this graphic representation, the differences in the abnormal from the normal are much more easily visible in the work and power tracing than in the force tracing.

* Electronics for Medicine, White Plains, New York.

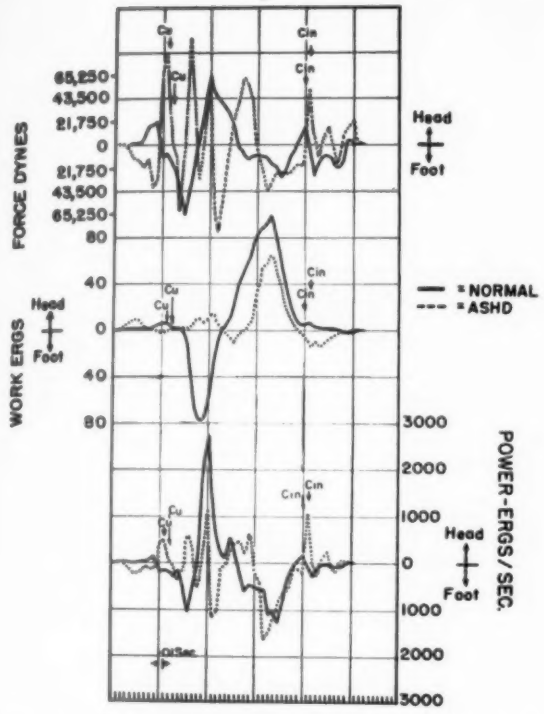

Fig. 3. This represents an example of a normal force, work, and power ballistocardiogram in contrast to a patient with arteriosclerotic heart disease in whom the force ballistocardiogram was of greater absolute value than that of a normal subject. The first CU represents the upstroke in the carotid pulse in the normal patient, while the second CU represents that of the patient with arteriosclerotic heart disease. CIN represents a carotid incisural notch in the two subjects respectively. Note that there is an absolute increase in peak forces in the tracing from the patient with angina pectoris; however, there is considerable reduction in the work and power tracing as contrasted to that of the normal subject. The work curve is not only decreased in absolute amplitude but there is an absence of the initial early footward work. Similarly, the power tracing from the patient with arteriosclerotic heart disease is considerably distorted both in configuration, as well as showing a decrease in the power. The peak forces, as noted in the patient with arteriosclerotic heart disease which are abnormal and of larger amplitude than that of a normal subject, are of such brief duration that they apparently accomplish very little work. This possibly illustrates an example where peak amplitudes or force units alone could give the impression of a heart with normal force; however, the abnormality would be as easily detected by the work and power units which show a marked decrease as compared to that of the normal subject.

variations of the abnormal from the normal. Although work is a scalar quantity, it is represented in the figure as having a headward and footward direction for graphic demonstration since the work measured is actually occurring either in a headward or footward direction (as measured by this technic). Note that the maximum J work and total work in the trace from the patient with angina pectoris is considerably reduced as compared to the normal. Similarly, a power trace can be constructed which represents the instantaneous power by multiplying the force at any instance by the velocity (formula 8). Figure 2 also includes the constructed power ballistocardiogram from the same normal subject, as well as from the same patient with angina pectoris to illustrate the possible differences in the abnormal situation. In addition, Figure 2 includes a calibrated force ballistocardiogram (acceleration trace converted into dynes) so that it may be read in absolute units in order to correlate the work and power trace with that of the force.

Figure 3 is an additional example of force, work and power ballistocardiogram from the same normal subject, as illustrated in Figure 2, as contrasted with the traces from another patient with angina pectoris. Note in this instance, the force ballistocardiogram of the patient with angina pectoris in terms of maximum deflection or amplitude is actually greater than that of the normal subject, while the work and power traces are considerably decreased in amplitude, abnormal in pattern, and the peak forces are reached at different times as compared to the normal traces.

The measurements just described were made only in the head-foot direction; therefore, a more accurate determination of work, and possibly power, could probably be determined from a three-dimensional ballistocardiographic bed. As three-dimensional ultra-low frequency ballistocardiograms are not yet available, total work and power cannot be estimated by this method at present. However, observations on a two-dimensional system have revealed that at least in many normal instances the work in the lateral direction is considerably smaller than that in the head-foot direction and may be negligible. Figure 4 illustrates the force, work, and power ballistocardiogram in both the head-foot and lateral positions in a normal subject. Although the peak forces in

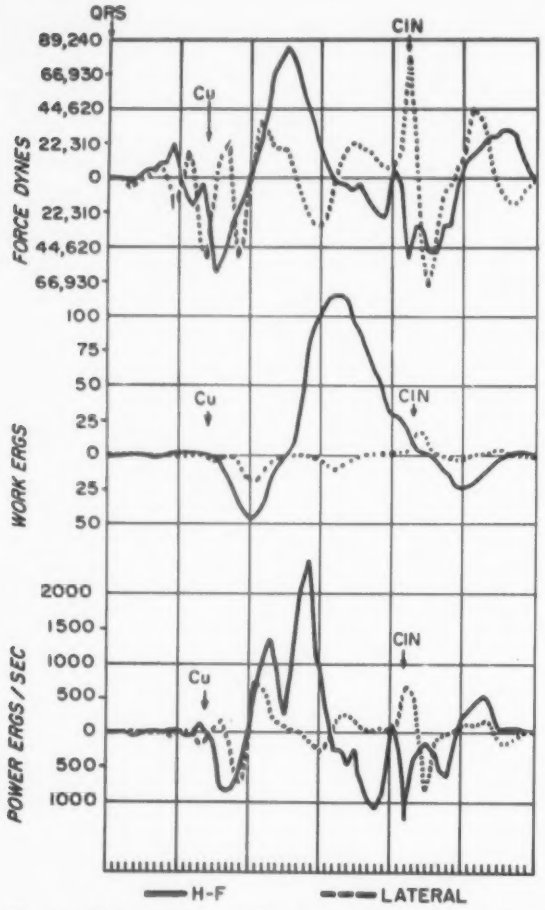

Fig. 4. This represents the force, work, and power ballistocardiograms in a normal subject, both in the head-foot and lateral directions as taken on a two-dimensional ballistocardiographic bed. Note that there is very little work or power in the lateral direction in this normal subject; however, it is likely that these may be appreciable in patients with cardiovascular disease.

the lateral traces in many instances may be equal to that noted in the head-foot direction, their duration is relatively brief so that the first integral or velocity traces are of small amplitude, and consequently the work in the lateral direction is considerably smaller than that registered in the head-foot direction. Although, as stated, work and power units are not vectoral forces, they can be considered to have a vectoral representation since velocity was recorded in two dimensions (head-foot and lateral). Thus it is possible to construct a vectoral loop for the work and power ballistocardiogram, as illustrated in Figures 5 and 6.

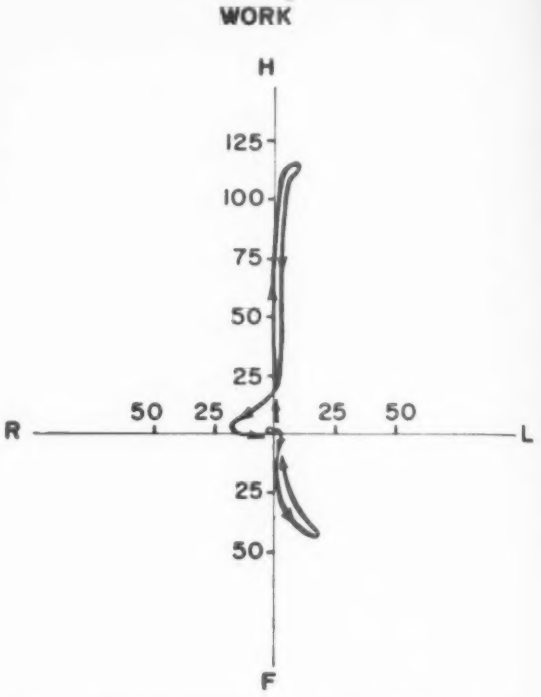

Fig. 5. This represents the frontal plane vectoral loop of the work curves. Only the systolic portion is represented in the diagram. Note that the major work in this normal subject occurs in the head-foot direction and very little is represented in the lateral. These values in ergs, as represented in this figure, are not considered to be absolute cardiovascular work, as explained in the text. Although work is a scalar quantity, and not vectoral, the loop is drawn for graphic purposes since work is measured in two axes.

Again note that the work loop has very small lateral representation compared to that registered in the head-foot direction. The full significance of these loops is not yet apparent.

Work and power associated with the cardiac cycle may be represented graphically in a different way without regard to direction. Figure 7 illustrates the force, work, and power during a cardiac cycle in the head-foot axis, as determined from the head-foot ballistocardiogram without reference to direction. The preceding figures illustrate the many types of analyses which can be applied to ballistocardiographic curves.

Discussion

The foregoing description points out a multidirectional approach, based primarily upon standard physical principles in which any bal-

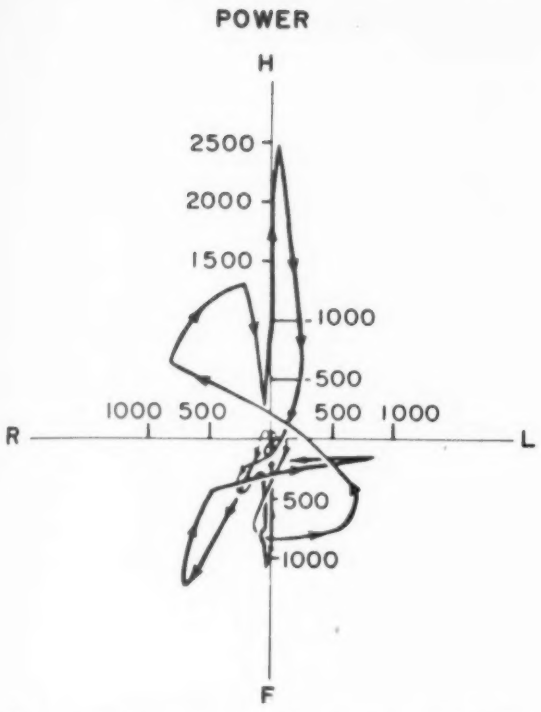

Fig. 6. This represents the power vectoral loop of a normal subject. This is included to illustrate the possible application of two-dimensional power ballistocardiograms. Only the systolic portion of the cardiac cycle is included in this figure. The power is first directed in the footward direction which immediately then is directed toward the left, followed by the two headward peaks. The complex portion of the loop in the footward right-hand quadrant represents the terminal portions of systole.

listocardiographic complex may be analyzed regardless of its configuration. The validity of this type of approach depends primarily upon the assumption that the ballistocardiogram is a complex repetitive waveform. This is not an unreasonable assumption since all of the physical principles which have recently been described for the ultra-low frequency technic are derived from standard vibratory physical formulae that are based primarily upon this assumption.

The most important question which arises in considering these calculations of work and power is whether the results accurately represent true cardiovascular work and power. This is a difficult question to answer; however, it is probably true that the absolute values obtained are not numerically the same as those for true cardiovascular work and power.

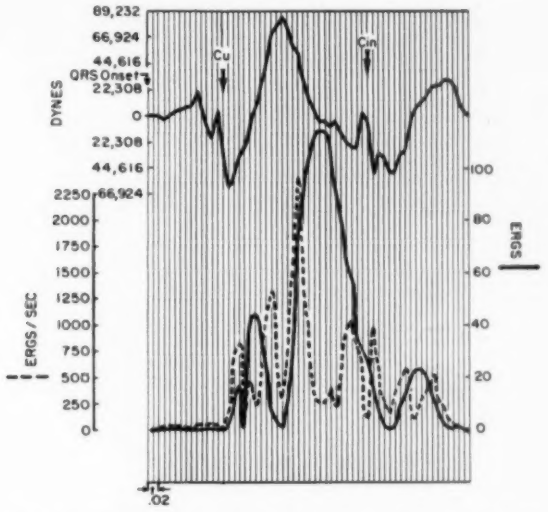

Fig. 7. This illustrates the force, work, and power ballistocardiogram with the work and power drawn only in one direction as scalar quantities. Note that there are two major peaks of work occurring in early and late systole and similarly three major peaks of power in the power graph.

There are several reasons for this: (1) The present method measures the effective work only in one or two axes (head-foot and lateral); (2) the values as calculated probably are not absolute heart work and power as they do not account for work of the heart which is lost through heat or friction. Therefore, they probably represent more closely the *net* effective work. Actually, work and power as calculated represents that associated with *the shift in the common or circulatory center of gravity.* (3) Recent theoretic consideration of the ultra-low frequency ballistocardiogram, by Noordergraaf,[9] has shown that the acceleration, velocity, and displacement ballistocardiograms are equal to the acceleration, velocity, and displacement of the common center of gravity. Since these are equal, then any calculations based upon the velocity or acceleration curves would be equal to the force, work, and power associated with the shift in center of gravity. From this theoretic consideration, the force ballistocardiogram does not necessarily indicate true cardiovascular force, but a force associated with this shift in the center of gravity.

From a physiologic standpoint, it is difficult to interpret what exactly is causing the shift in the center of gravity. Undoubtedly, it is

due at least in part to the movement of blood or the repositioning of blood as the result of ejection and changes in position of the heart and its attachments.* Thus the resultant curves, in essence, represent the over-all net effect of these changes in the axis chosen to record the ballistocardiogram. The complex can be subdivided into the pre-ejection, ejection, and isometric relaxation phases for further physiologic considerations. In this instance, the work and power, during the pre-ejection phase, must therefore represent shifts in the center of gravity as the result of heart movement as there is no ejection taking place. During ejection, the largest power exerted is early, or during the time when blood is being rapidly accelerated, while the greatest magnitude of work is accomplished during late ejection, or when there is actually a considerable decrease in the rapidity and volume of blood leaving the heart (Fig. 2). Thus the early ejection phase may be much more indicative of myocardial strength, while the terminal phase may be more indicative of peripheral blood flow. Similarly, isometric relaxation should indicate the forces, work, and power associated with the relaxation phenomena and movements of the heart, rather than those due to blood flow.

Obviously, correlations in the experimental animal with heart work determined directly with work and power, as measured by the ballistocardiogram, must be carried out. Nevertheless, even if these calculations do not entirely parallel the true values of heart work and power, this method of approach appears to be potentially useful. Preliminary observations suggest that patients with myocardial disease have a diminution in the work and power ballistocardiogram, while patients in whom work and power are expected to be increased, such as aortic insufficiency, thyrotoxicosis, and arteriovenous fistulas, do show a marked increase.†[6] In addition, the technic offers a consistent method of analysis by which any ballistocardiogram, normal or abnormal, and without regard to its configuration, can be analyzed. Also, many drugs and physiologic stresses can be investigated to determine their effects on the heart and cardiovascular system in terms of force, work, and power. This type of study promises to offer information not generally available by other methods.

* Displacement or movements of the liver could possibly contribute to the ballistocardiogram.

† Although amplitude is increased in these disease states using conventional ballistocardiograms, little quantitation is possible.

Summary and Conclusions

(1) A new multi-directional approach to the analysis of the ballistocardiogram is presented, based primarily on physical principles. Force, work, power, and impulse can be calculated from the ballistocardiogram regardless of the configuration or abnormality.

(2) These calculations primarily reflect the force, work, and power associated with shift of the common center of gravity, as measured in the head-foot axis.

(3) Examples of the force, work, and power ballistocardiograms are presented, based on the head-foot and lateral axes.

(4) It appears that the calculations offer a useful means by which a ballistocardiogram can be consistently interpreted, and it is possible that this technic offers a new approach in the study of many pharmacologic, as well as physical effects on the heart and circulatory system.

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Review

Aneurysms of the Thoracic Aorta

Review of Diagnostic and Etiologic Features*

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ADVANCES in cardiovascular surgery permitting the repair of aneurysms have made recognition of aneurysms of the thoracic aorta of practical importance; a review of their diagnoses and etiologies is, therefore, timely. Aneurysms of the ascending portion of the thoracic aorta, a site previously inoperable, can now be successfully treated.[1] Aneurysms of the aortic arch, proximal or distal to the brachiocephalic branches have also been sutured[2] and resected with the use of shunts and replacement by homografts.[3,4] Even ruptured aortic sinus aneurysms formerly inaccessible because of their intracardiac location have been sutured using open heart technics.[5]

The symptoms caused by aneurysms of the thoracic aorta are often due to their location and disturbance of neighboring structures. For instance, unperforated sinus aneurysms may exist and go unnoticed for years and become catastrophic only when rupture occurs.[6] Aneurysms of the ascending aorta may also cause few symptoms until there is dilatation of the aortic ring or associated disease of the aortic valves resulting in aortic insufficiency, left ventricular strain, hypertrophy, and heart failure. On the other hand, aneurysms of the aortic arch, because of pressure effects on closely related vital structures, usually produce alarming symptoms which bring patients to the physician. Hoarseness may be caused by recurrent nerve paralysis; dyspnea by tracheal or bronchial compression; dysphagia by esophageal constriction; and chest pain by thoracic vertebral body erosion. In marked contrast, are the descending aortic aneurysms

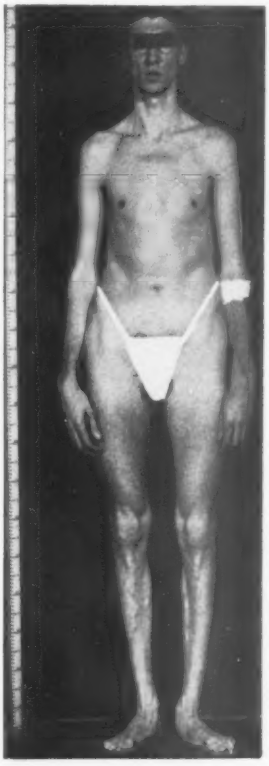


Fig. 1A. Aneurysmal dilatation of the aortic sinuses in a 23-year-old man with Marfan's syndrome. The heart was normal in size and only an apical systolic murmur and thrill were found. This photograph showing the typical long, thin habitus of Marfan's syndrome. Bandage over eyes masks glasses containing thick lens correcting myopia.

* From the Departments of Radiology and Medicine, The New York Hospital-Cornell Medical Center, New York, New York. Aided by a grant from the Mallinckrodt Chemical Works.

which usually do not cause discomfort and are, therefore, discovered only after routine chest roentgen examination.

For purposes of review, aneurysms of the thoracic aorta may be classified according to their etiology: congenital, unknown, infectious, degenerative (arteriosclerotic) and traumatic.

Congenital Aneurysms of the Thoracic Aorta

Congenital aneurysms of the thoracic aorta may occur in any portion;[7,8] a favorite location appears to be the aortic sinuses. In Marfan's syndrome, a heritable disease of connective tissue,[9] medial degeneration of the aorta may cause aneurysmal dilatation of the aortic sinuses.[10] Associated dilatation of the aortic ring may then result and be followed by aortic regurgitation and heart failure. Rupture and dissection of an ascending aortic aneurysm are also frequent in this disease.

Angiocardiography permits the demonstration of aortic sinus aneurysms in Marfan's disease during life.[11] A total of nine patients, including a set of twins[12] with this disorder have been diagnosed. In two of the nine cases, there was no cardiac enlargement. Figures 1A and B show the characteristic slender, thin habitus and arachnodactyly in Marfan's syndrome. Figures 1C and D reveal the aneurysmal dilatation of the aortic sinuses.

Aneurysmal dilatation of the aortic sinuses has also been demonstrated angiocardiographically as an isolated lesion and in association with coarctation of the aorta (Fig. 2A and B) and aortic and mitral valvular murmurs.[17] Myxomatous changes of the cardiac valves have been found frequently associated with congenital cardiovascular disease and may be responsible for

Fig. 1B. Note the long, thin and tapering fingers.

Fig. 1C. Left anterior oblique angiocardiogram showing aneurysmal dilatation of the aortic sinuses (arrow).

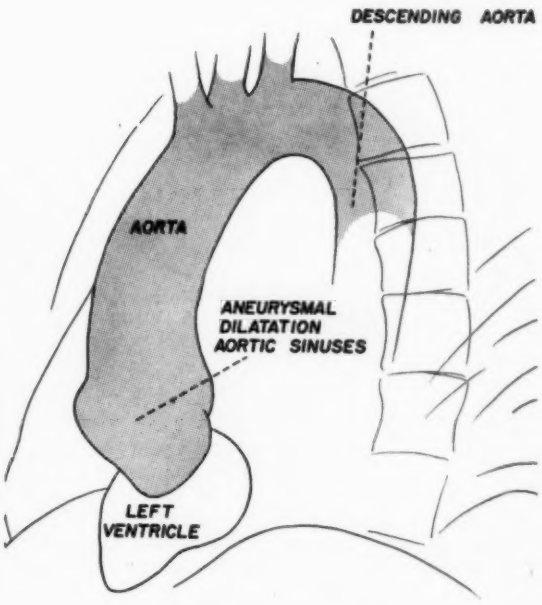
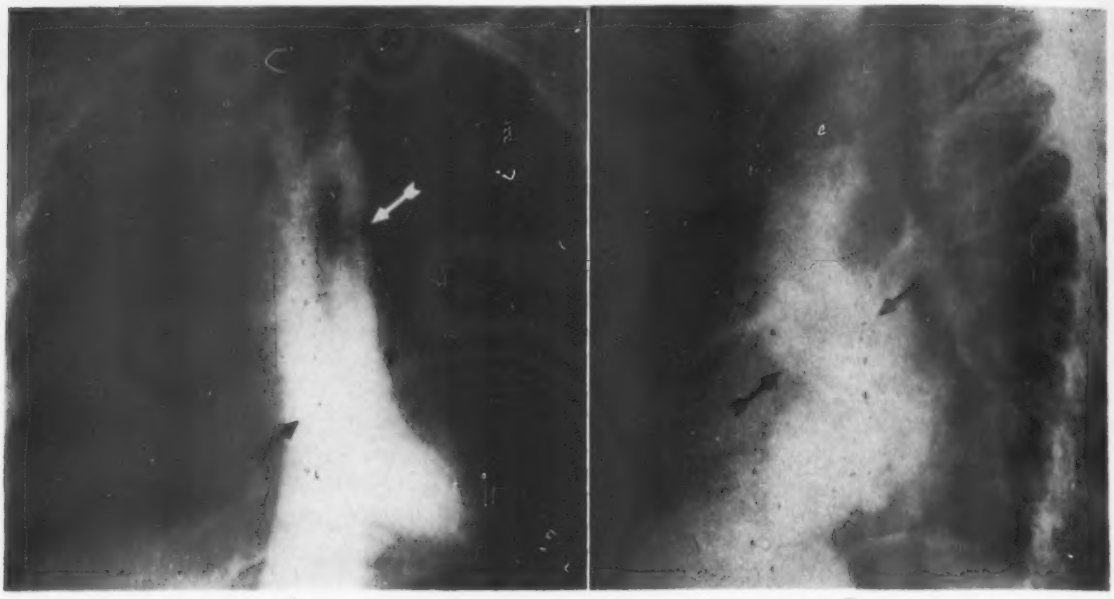


Fig. 1D. Tracing of C.



A B

Fig. 2. Aneurysmal dilatation of the aortic sinuses associated with coarctation of the aorta in a 14-year-old boy with mild upper extremity hypertension and absence of leg blood pressures. A cardiac murmur was present. (A) Frontal angiocardiogram showing the aortic sinus aneurysmal dilatation (enclosed by arrows) and the point of coarctation (arrow) of the descending aorta beyond the left subclavian artery. (B) Left oblique angiocardiogram also reveals the aortic sinus aneurysm (arrows) and the aortic coarctation (arrow).

murmurs.[12] However, in a recent case studied at necropsy calcific aortic stenosis of probable rheumatic etiology complicated a ruptured aortic sinus aneurysm. Aneurysmal dilatation of the aortic sinuses in a 14-year-old girl with a continuous murmur to the right of the sternum and with increased oxygenated blood in the right ventricle on cardiac catheterization, believed to be due to a small aortico-cardiac rupture, is illustrated in Figure 3.

Fig. 3. Perforated aortic sinus aneurysm in a 14-year-old girl with a continuous murmur along the right lower sternum. Cardiac catheterization disclosed a 0.6 per cent increased oxygen content in right ventricle. Frontal angiocardiogram discloses aneurysmal dilatation of the aortic sinuses (arrows). The left ventricular cavity (LV) is slightly enlarged. (Studied at St. Francis Hospital and Sanatorium, Roslyn, N. Y.).

Thoracic Aneurysms of Unknown Etiology

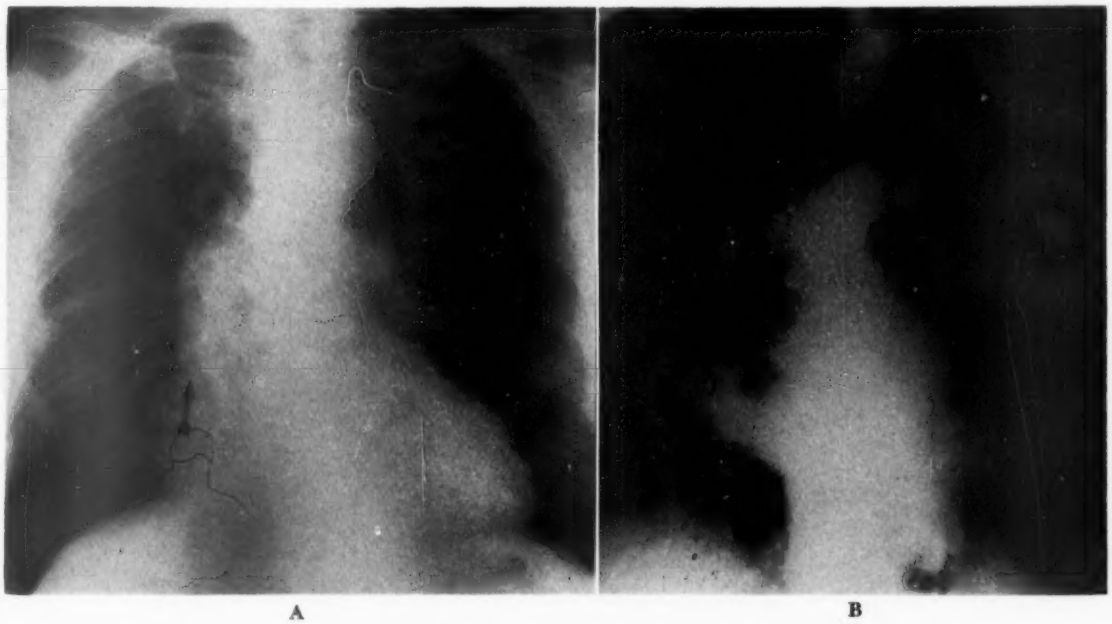
Medial cystic necrosis of the aorta (Erdheim's cystic medionecrosis) may lead to aortic rupture and dissection. Several series in young adults have been described in the medical and pathologic literature.[18,19] During life several patients with congenital aneurysms of the aorta diagnosed by angiocardiography have been reported but whether these are associated with medial cystic degeneration is unknown.[7,8] Figure 4 is an ascending aortic aneurysm in a 38-year-old patient. The aneurysm is believed to be congenital because of onset in early life; syphilis was excluded by serologic studies.

Fig. 4. Congenital aneurysmal dilatation of the ascending aorta in a 46-year-old man with negative serology and history of aneurysm of 20 years' duration. Recent development of bouts of paroxysmal atrial tachycardia led to angiocardiographic study. Left anterior oblique angiocardiogram shows the huge ascending aorta aneurysm (arrows).

Thoracic Aneurysms Due to Infection

Formerly, the commonest cause of thoracic aneurysms was syphilis. Fortunately, penicillin therapy is effective in preventing the development of cardiovascular syphilis so that in the near future syphilitic aneurysms will become a rarity. Syphilitic aneurysms can occur in any portion of the aorta, but the ascending aorta, probably because of the rich vascular bed, is the usual site. Syphilitic aortitis is often followed by aneurysmal dilatation of the ascending aorta. This with invasion of aortic commissures results in aortic regurgitation. In some instances aneurysmal dilatation of the aortic sinuses also occurs[20] and the conventional roentgenogram disclose widening and calcification of the ascending aorta. Angiocardiography is very effective in establishing the early diagnosis of syphilitic aortitis[21,22] and is especially useful in the diagnosis of syphilitic aortic sinus aneurysms (Fig. 5).[20]

Figure 6 shows a syphilitic aneurysm of the innominate artery that caused severe dyspnea because of tracheal compression. Angiocardiog-



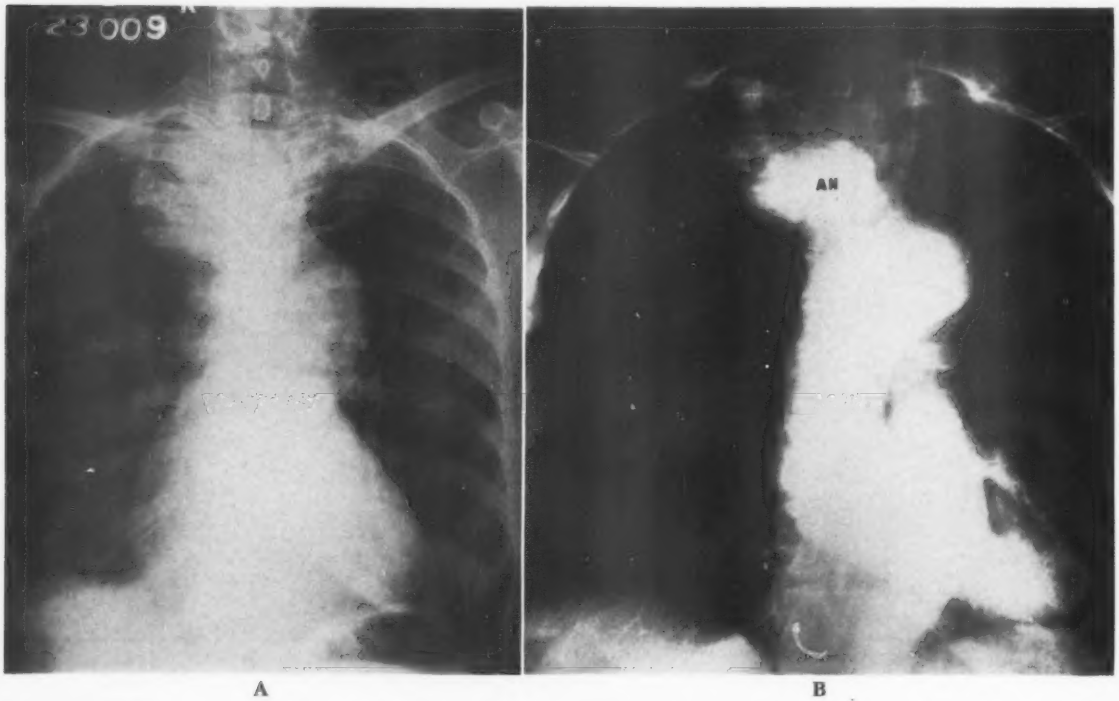
A B

Fig. 5. Syphilitic aneurysm of the ascending aorta involving the aortic sinuses in a 55-year-old man with positive blood serology and with signs of aortic regurgitation. (A) Conventional frontal roentgenogram reveals enlargement of the left ventricle. The ascending aorta is markedly dilated and contains calcium at the root of the aorta (arrow). (B) Frontal angiocardiogram at 4 seconds reveals a filling defect of the right atrium caused by the aortic aneurysm involving the aortic sinuses.

Fig. 5C. Left anterior oblique angiocardiogram shows aneurysmal dilatation of the ascending aorta including the aortic sinuses (arrows).

raphy by outlining the extent of the disease permitted the preoperative selection of a proper homograft. In another patient (Fig. 7) erosion of dorsal vertebrae produced kyphosis of the spine. Visualization of the aortic arch aneurysm disclosed a saccular and localized lesion of the arch. Since the left subclavian artery was intact, resection of the aneurysm without the need of providing a shunt for cerebral circulation was possible.

Rarely, mycotic aneurysms due to tuberculous or bacterial endocarditis may cause aortic aneurysms. Thoracic aneurysms due to rheumatic aortitis are also very rare. Figure 8 shows a huge aneurysm of the ascending aorta in a patient with aortic and mitral valvular disease. Death was due to rupture of the aneurysm. At necropsy Aschoff lesions could not be demonstrated in the aorta or valvular lesions. Syphilitic and arteriosclerotic lesions were also absent in the ascending aorta. Because of the history of rheumatic fever and the advanced aortic and mitral valvulitis that produced stenosis and re-



A B

Fig. 6. Syphilitic aneurysm of the innominate artery in a 63-year-old woman. (A) Conventional frontal roentgenogram shows a huge mass in the superior mediastinum compressing the trachea. The aortic knob is also prominent and contains calcium. (B) Frontal angiocardiogram reveals a huge innominate artery aneurysm (AN) with surrounding thrombus.

Fig. 7. Syphilitic aneurysm of the aortic arch eroding thoracic vertebral bodies, causing kyphosis in a 48-year old man. Arrows point to the aneurysm in the left anterior oblique angiocardiogram. The left subclavian artery (LSA) is intact permitting resection of the arch without the use of a shunt for the cerebral circulation.

gurgitation and resembled rheumatic disease, the diagnosis of rheumatic aneurysm seemed warranted.

Arteriosclerotic Aneurysms of the Thoracic Aorta

Arteriosclerosis of the thoracic aorta tends to occur in the arch and descending portions of the aorta. This is in contrast to syphilis, where the ascending aorta and arch are usually involved, and is explained by spirochetal localization in the aortic root and ascending aorta because of the abundance of vasa vasorum in these regions. Syphilis causes destruction of all elements of the arterial wall, the elastic and muscle fibers of the media, and severe vasa vasorum endarteritic lesions producing anoxia of the wall and aneurysmal dilatation. In addition, involvement of the aortic valves by the syphilitic process and the development of aortic regurgitation cause increased cardiac output and often systolic hypertension. These stresses favor development of aneurysms of the ascending and transverse portions of the aorta.

Due to the decreasing incidence of tertiary syphilis and increased life expectancy, aneurysms of the thoracic aorta are now more commonly due to arteriosclerosis than to syphilis.[23] The pathologic mechanisms responsible for the formation of the arteriosclerotic aneurysm are not entirely clear. De Takats and Pirani[24] believe that the following local factors are of prime importance in the formation of arteriosclerotic aneurysms: deposition of fibrin and hematogeneous substances in the intima; accumulation of ground substances and disruption of elastic lamellae in the media; and disturbance of circulation in the vasa vasorum. Atheroma formation, probably due to faulty lipid metabolism, may further weaken the arterial wall, form atheromatous ulcers and cause dilatation. Indeed, mural thrombus formation and fibrosis of the arterial wall and periarterial tissues are attempts to stay the progress of dilatation. The aneurysmal tendency also depends upon the level of systolic pressure, direction and force of secondary blood currents, and the state of the vascularization of the aneurysmal wall. It is the latter factor that appears to be the most important and yet least understood, although there is general agreement that the walls of aneurysms are poorly vascularized. As a result, the fibrous tissues replacing the elastic and muscle fibers are defective and inadequate and even mural thrombi are only partially organized.

Recently a series of six patients with arteriosclerotic aneurysms of the thoracic aorta was reported.[25] A patient with generalized arteriosclerotic dilatation of the thoracic aorta involving the sinus of Valsalva is demonstrated in Figure 9. A dissecting aneurysm of the thoracic aorta is shown in Figure 10.

Traumatic Aneurysms of the Thoracic Aorta

Aneurysms of the thoracic aorta due to blunt trauma although rare, occur more frequently than suspected. This is because increasing speed of the present vehicular era has made accidents commonplace. Formerly, the diagnosis of aortic rupture during life was rarely made; multiple fractures and internal injuries associated with profound shock overshadowed the thoracic injuries and the chest was overlooked.

Rupture of the thoracic aorta due to blunt

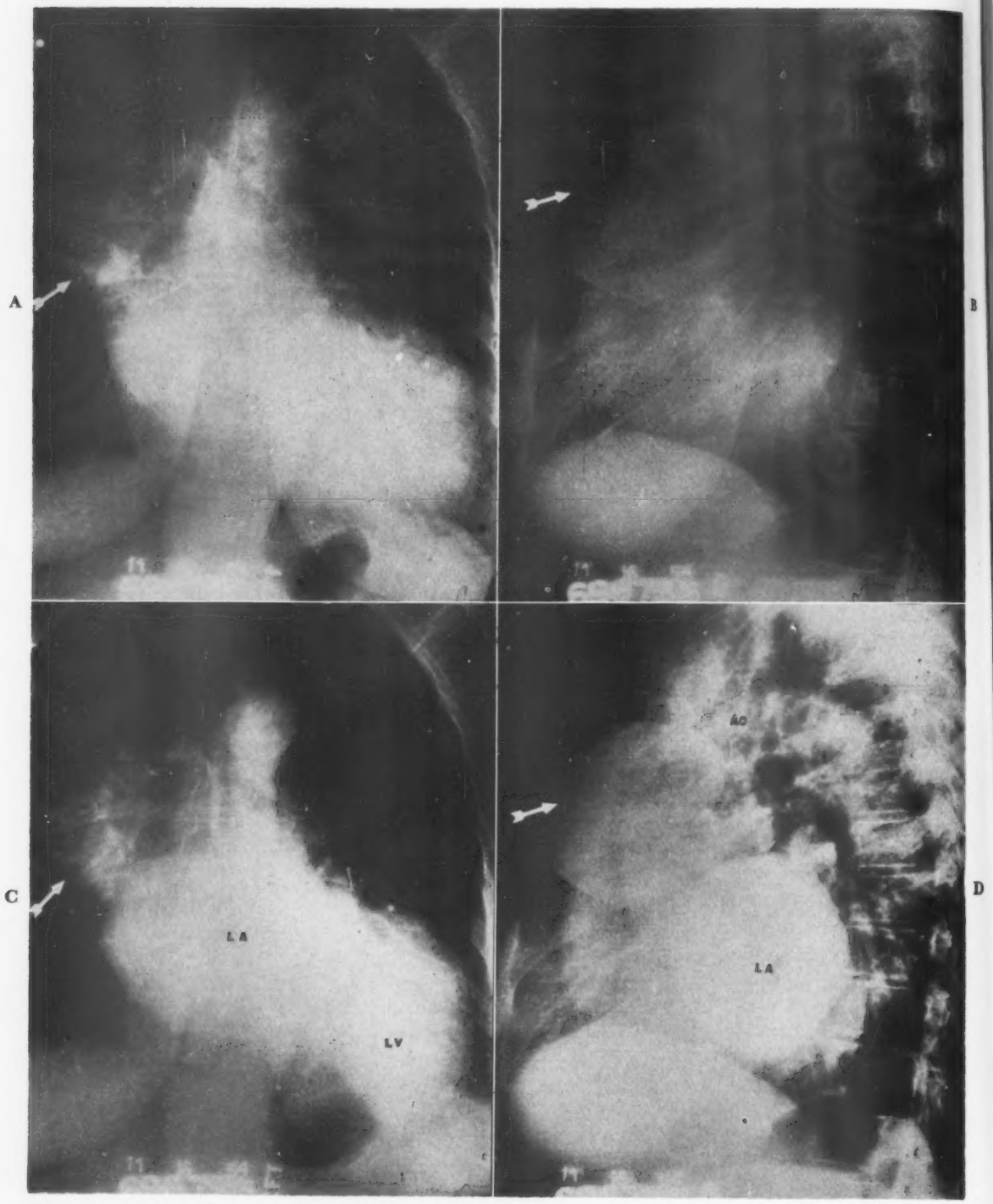


Fig. 8. Aortic aneurysm due to rheumatic fever in a 53-year-old woman with advanced aortic and mitral valvular disease. (A) Overpenetrated conventional roentgenogram shows a huge calcium lined mass (arrow) in region of the ascending aorta. The left atrium and ventricle appear enlarged. (B) Lateral roentgenogram also shows the calcified mass (arrow) to be closely related to the ascending aorta. Note the prominent left ventricle. (C) Frontal angiocardiogram at 17 seconds reveals an opacified huge left atrium (LA); the left ventricle (LV) is also large and the mass (arrow) is faintly opacified. (D) Left anterior oblique angiocardiogram also shows the large left atrium (LA). The aorta (AO) including the ascending aortic aneurysm (arrow) is also opacified.

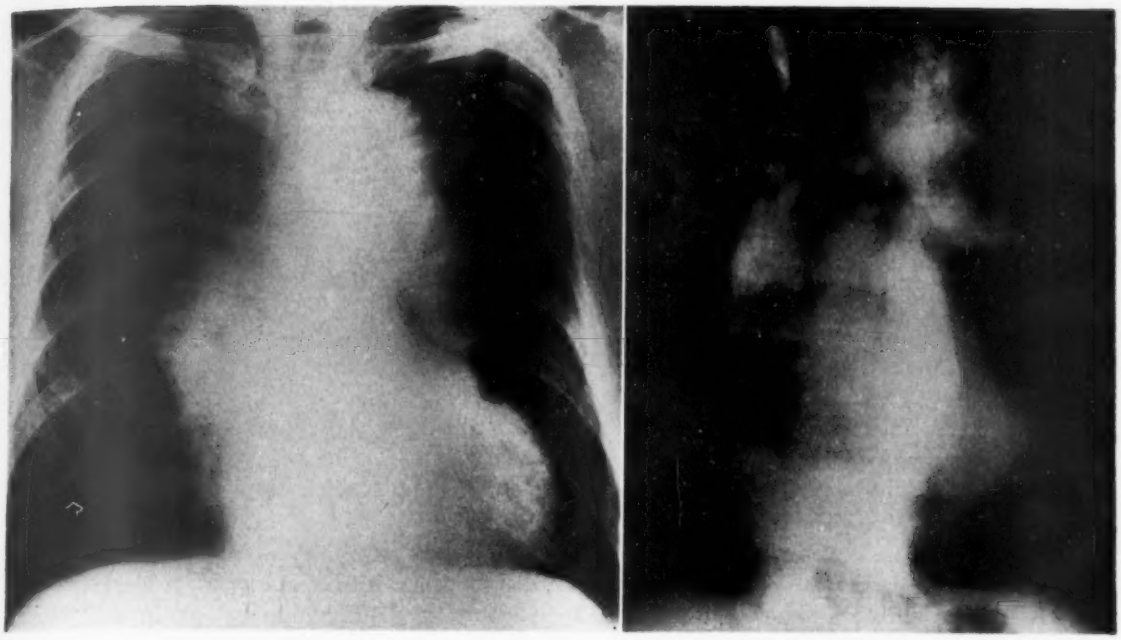


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Fig. 9. Aneurysmal arteriosclerotic dilatation of the thoracic aorta including the aortic sinuses in a 55-year-old man with negative blood serology. (A) Conventional frontal roentgenogram shows enlargement of the heart and ascending aorta. (B) Frontal angiocardiogram reveals a huge filling defect of the right atrium due to aneurysmal dilatation of the aortic sinuses.

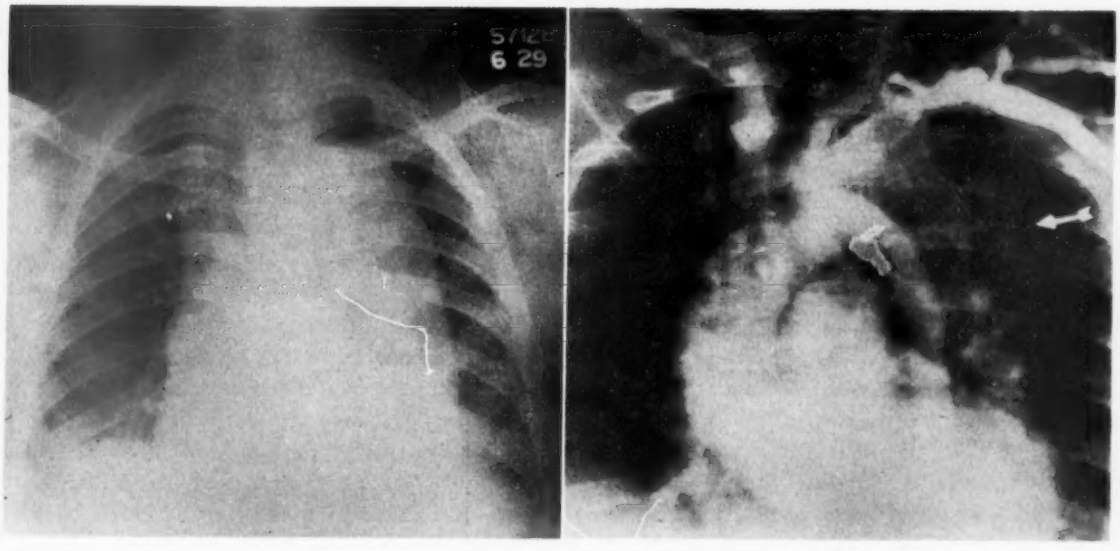

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Fig. 10. Chronic dissecting aneurysm of the descending aorta in a 49-year-old woman with hypertension and a history of severe chest pain 3 years previously. (A) Conventional frontal roentgenogram reveals a hugely dilated thoracic aorta. (B) Frontal angiocardiogram shows a "double lumen" deformity of the descending aorta. Arrow points to the outer aortic wall. Medially, there is opacified material in a false channel surrounded by thrombus. The descending aorta is markedly narrowed.

trauma occurs most frequently at the top of the aorta.[26] This is explained by the physical forces which are concerned with deceleration, acting with undue stress on the aorta, producing a tear just beyond the point of fixation by the brachiocephalic arteries and the insertion of the ligamentum arteriosum. Strassmann,[27] in a classic report of 72 cases of aortic rupture among 7,000 autopsies from the files of the Chief Medical Examiner's Office of the borough of Manhattan of New York City during the years 1936 to 1942, found that the majority of the cases occurred at the top of the aorta; 20 per cent occurred at the ascending aorta just above the cusps; and 20 per cent in the descending aorta from the isthmus to the diaphragm. In all but eight subjects, the aortic rupture was through-and-through and involved all the layers of the aorta. In the eight cases, rupture was incomplete; the adventitia being preserved and dissected from the medial layer by thrombus. When all the layers of the thoracic aorta are torn, fatal hemorrhage usually results. In a few, especially when the adventitia is spared, there may be organization of the thrombus with a connective tissue wall and formation of a false aneurysm with recovery.

Aneurysms of the thoracic aorta following blunt trauma may be divided into the acute and chronic types. In the acute stage, unconsciousness, shock, multiple fractures, and internal injuries may divert attention away from the thorax and result in overlooking aortic rupture. Recently several authors have stressed the importance of routine serial chest roentgenography following injuries. This has resulted in the diagnosis of aortic rupture during life and provided an understanding of the course of events in the patients that survive. At first, there is widening of the mediastinum and obscuration of the arch of the aorta with fluid formation in the left chest due to mediastinal hematoma and hemothorax. Later, in a few days to three to four weeks, a vague bulge appears adjacent to and indistinguishable from the aortic knob; the aneurysm later becomes localized and distinct. Such was the course of events in a patient who was observed from the onset of injury.[28] In four patients recently studied[29] and in many cases reported in the literature[30] the diagnosis of chronic aneurysm of the aorta was made only after a chance roentgenogram disclosed a mediastinal mass (Fig. 11). In some patients, symptoms such as dyspnea, cough, and pain in the chest cause them to seek medical aid. The characteristic site of the aneurysm at the top of the descending aorta should suggest the diagnosis; a history of chest trauma confirms it.

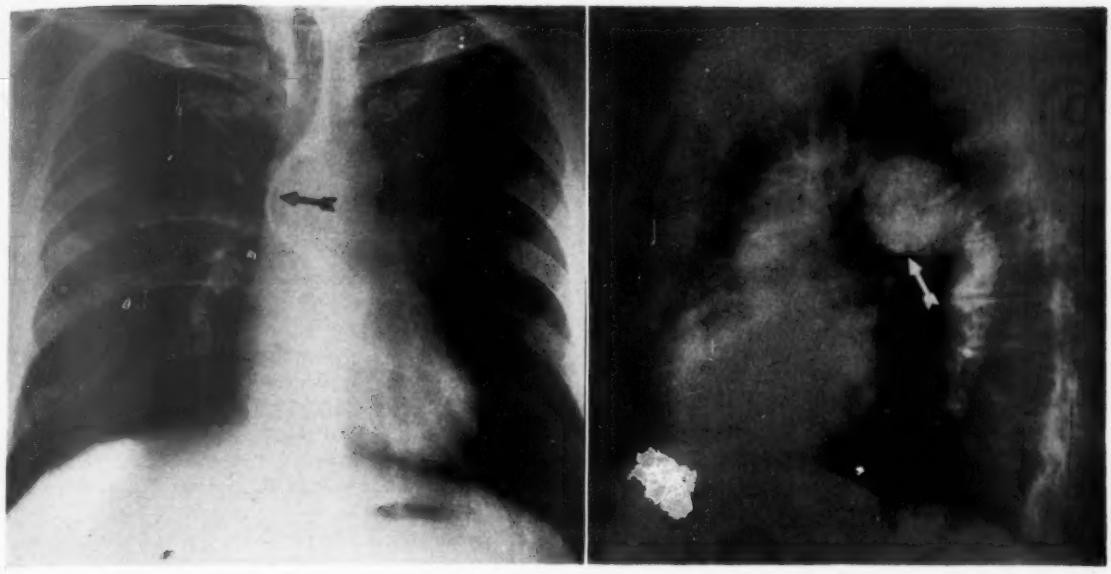
Comment

Conventional roentgenography of the chest by disclosing hilar or mediastinal masses or enlarged aortic shadows provides significant clues for the diagnosis of aortic aneurysms. Fluoroscopy is also valuable for localizing aneurysms. Study in the left anterior oblique position, which allows a lateral view of the aorta and separates it from the heart, is especially important for differentiating aortic unfolding, tortuosity and dilatation.[31] Calcification of the aortic wall and aneurysm is frequent. Generalized aortic density, a sign of thickening and sclerosis, also occurs. Esophageal visualization with barium aids in the demonstration and estimation of aortic tortuosity.

Except for a systolic murmur there are no significant diagnostic features for recognition of unperforated congenital aortic sinus aneurysms. Linear or massive calcifications in the intracardiac portion at the root of the aorta continuous with linear calcification of the ascending aorta occur often in syphilitic aortic sinus aneurysms. As a rule acquired aortic sinus aneurysms are larger than congenital. Accordingly, a high index of suspicion and angiocardiography are advocated for the diagnosis of aortic sinus aneurysms during life.

Angiocardiography, by visualizing the thoracic aorta, provides the definite diagnosis of aneurysm. In the normal, the opacified ascending aorta appears smooth and regular in outline. In contrast in syphilitic aortitis, the midportion of the ascending aorta is generally more than 38 mm in diameter, and is irregular.[21]

The diagnosis of arteriosclerotic aneurysms of the thoracic aorta may originate with routine roentgen study of the chest, especially in patients over 50 years of age. If hypertension is found and there are complaints of chest pain,



A B

Fig. 11. Chronic traumatic aneurysm in a 43-year-old asymptomatic man discovered after routine roentgenography of the chest. Aneurysm followed a severe automobile accident 21 years previously. (A) Frontal esophagram showing marked deviation of the esophagus by a calcium-lined mass (arrow). (B) Left anterior oblique angiocardiogram showing a saccular aneurysm (arrow) of the aortic arch beyond the origin of the left subclavian artery. Conservative treatment indicated because of the asymptomatic status. (From: STEINBERG, I.: *New England J. Med.* 257:943, 1957.)

roentgen study of the chest is mandatory. The finding of mediastinal or hilar masses related to the aorta, especially if pulsatile, should suggest the possibility of aneurysm. However, pulmonary and mediastinal tumors that are intimately related to the cardiac chambers or great vessels may also be pulsatile and simulate aneurysms. Unfolding, elongation, dilatation, and tortuosity of the aorta are common in hypertension and arteriosclerosis, and also need to be differentiated from aneurysms. Enlargement of the aorta due to dissecting aneurysm (dissection and hematoma) (Fig. 10) must also be considered. Aortic anomalies, especially of the arch, may also simulate aneurysms. For these reasons, and because exact delineation of the aneurysm will aid in planning the operative attack and selection of the proper size of the graft, angiocardiography is advocated.

Unlike abdominal aortic aneurysms, which are usually due to arteriosclerosis, the etiology of thoracic aorta aneurysms is difficult to determine, especially if the serologic test and history for syphilis are negative. The location of the aneurysm is of some importance. Aneurysms of the ascending and transverse aorta in the younger age groups are usually syphilitic; however, aortic dilatation of the ascending portion may occur in hypertension and rheumatic aortitis. The arteriosclerotic process usually involves the transverse and descending aorta and spares the ascending portion. The presence of a smooth, undilated and regular ascending aorta on angiocardiography does not rule out syphilis unequivocally. However, such findings are uncommon in syphilitic aortitis.

The diagnosis of acute traumatic aneurysms of the thoracic aorta depends upon a high index of suspicion in every severe injury even though there is absence of external thoracic bruises. Early, following automobile accidents, serial roentgenograms may reveal evidences of bleeding by progressive mediastinal widening, obscuration of the aortic arch, increased aortic density or layering due to hematoma. This may be followed by a localized bulge of the beginning of the descending aorta. Later, in the chronic phase, there is a well circumscribed mass adjacent to the aortic knob. Chronic traumatic aneurysms of long standing often con-

tain calcium deposits in the walls. Contrast visualization of the thoracic aorta by the method of angiocardiography readily establishes the diagnosis of aneurysm. Other aneurysms at the top of the descending aorta (syphilitic, arteriosclerotic, and congenital) need to be differentiated from the traumatic. The syphilitic are usually associated with aortitis; the irregular dilated and calcific ascending portion of the aorta often accompanies syphilitic aneurysms and is also readily discernible after angiocardiography. Finally, a positive serologic test for syphilis is confirmatory. Arteriosclerotic tortuosity of the aortic knob and buckling of the brachiocephalic arteries may sometimes simulate aneurysms and are readily disclosed by angiocardiography.[31] Lastly, congenital anomalies of the aorta, such as the kinking associated with dilatation of the left subclavian artery (pseudocoarctation) may be mistaken for aneurysms; roentgenography, especially angiocardiography, readily establishes the congenital nature of the deformity.[32] In the acute stages of aortic rupture a mediastinal hematoma may simulate mediastinal tumors or effusions. Traumatic mediastinal hematomas also result from bleeding of neighboring venous channels. Tumors of the mediastinum may readily be differentiated from aneurysms by angiocardiography and, of course, are not associated with accidents.

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Report on Therapy

The Management of Moderately Severe Hypertension with Cryptenamine and Rauwolfia*

Observations in Patients Treated for Up to Two Years

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> "I immediately gave her fifteen drops of Veratrum viride and directed that she should take ten more in two hours . . . she was not even nauseated, although the medicine was given at regular intervals during the whole night."
>
> Baker, 1859[1]

THE VIRTUES of veratrum as an "arterial sedative" were well known more than a century ago.[2] In 1859 Baker[1] reported the efficacy of "Veratrum viride in chorea and other convulsive disorders," although the characteristic fall in blood pressure was not documented for another 50 years.[3] The passage of time has confirmed the hypotensive potency of the veratrum alkaloids.[4–6] Despite this considerable experience, the role of veratrum in the management of the patient with arterial hypertension remains uncertain. The pertinent literature reflects a considerable divergence of opinion concerning the degree of vasodepression obtained with oral therapy, some investigators observing a "significant" drop in blood pressure in from one-half[7] to three-quarters[8] of the patients treated, while an unimpressive response has been noted by others.[9] In contrast to this, the effects obtained by the parenteral route have been dramatic and often life-saving.[10] The great frequency of side-reactions, approaching an incidence of 100 per cent in some evaluations,[11] has been an additional factor qualifying chronic use. For these reasons, veratrum has been reserved chiefly for the regulation of a variety of hypertensive emergencies on an acute basis.[10,12–15]

In 1954 attention was first directed to cryptenamine, a newly prepared alkaloid of veratrum viride, which had been demonstrated in the laboratory to have a ratio of 4:1 in regard to hypotensive and emetic dosages when given intravenously.[16] Treatment of a small number of ambulatory hypertensive patients,[17] and later of a somewhat larger group,[18] suggested the usefulness of oral cryptenamine. The addition of reserpine, a rauwolfia alkaloid, enhanced the cryptenamine-induced depressor response and ameliorated side-effects from the latter.[18,19] In view of this, it seemed of interest to assess the possible role of cryptenamine in long-term treatment. It is the purpose of this communication to present clinical observations made in 41 individuals with arterial hypertension treated with cryptenamine alone or cryptenamine-reserpine

* From The Elizabeth General, St. Elizabeth's and Alexian Brothers' Hospitals, Elizabeth, New Jersey.

TABLE I

Physiologic Response to Cryptenamine and Cryptenamine plus Reserpine in the Treatment of Arterial Hypertension

Patient	Age	Smith-wick group	Daily dose (mg)		Mean blood pressure*			Blood pressure			Months of treatment	
			Crypt-enamine	Reser-pine	Control	Crypt-enamine	Crypt-enamine plus reser-pine	Control	Crypt-enamine	Crypt-enamine plus reser-pine	Crypt-enamine	Crypt-enamine plus reser-pine
F. F.	67	4	14		173	96		240/140	130/80		9	
R. J.	63	3	10		153	110		210/125	150/90		10	
M. P.	67	4	12		163	106		220/135	150/85		14	
F. C.	64	3	14		163	108		210/140	145/90		10	
A. N.	64	3	8		140	98		190/115	135/80		23	
J. R.	56	3	8		155	123		205/130	160/105		17	
W. B.	66	3	14		146	110		200/120	150/90		23	
C. L.	51	3	8		153	116		200/130	150/100		18	
R. A.	49	3	12		153	116		210/125	150/100		17	
J. J.	58	2	10		150	116		210/120	160/95		22	
A. H.	59	3	12		136	130		210/100	180/105		18½	
S. P.	56	4	10		170	116		230/140	160/95		17	
C. B.	65	3	10		156	116		210/130	175/90		19	
R. F.	63	3	12		145	106		205/115	160/80		19	
B. N.	53	3	14		158	93		225/125	130/75		17	
J. K.	54	3	12		150	110		200/125	150/90		17	
J. G.	60	3	12		146	110		200/120	140/95		18	
E. L.	67	4	12		145	126		200/125	180/100		17	
A. C.	68	3	10		153	113		200/130	170/85		17	
A. L.	55	2	10		147	120		190/125	160/100		17	
F. V.	72	4	14		160	116		220/130	170/90		16	
A. W.	58	3	16		180	126		240/150	180/100		6	
M. B.	62	3	16		160	120		220/130	170/95		7	
Q. F.	66	4	10		167	103		240/130	140/85		7	
Cryptenamine alone			13		155	120		212/127	156/103		15½	
H. K.	62	4	10	0.10	166	126	120	250/140	180/100	160/100	1	9
G. K.	66	4	12	0.25	153	130	116	240/110	190/100	160/95	1	10
A. F.	63	4	10	0.10	156	126	88	210/130	190/95	115/75	1	14
H. J.	66	4	14	0.30	183	156	103	260/145	210/130	140/85	1	11
M. R.	55	4	12	0.10	163	130	96	230/130	190/100	130/80	1	9
C. M.	35	4	10	0.10	152	130	117	195/130	170/110	160/95	1	21
T. W.	51	3	12	0.25	146	150	120	200/120	190/130	160/100	3	16
A. T.	66	3	14	0.50	145	127	116	205/115	170/105	160/95	4	16½
G. R.	78	4	10	0.25	156	126	120	210/130	190/95	170/95	4	16
B. S.	63	3	14	0.10	160	130	120	250/115	190/100	170/95	2	17½
R. G.	52	3	14	0.25	141	136	113	205/110	190/110	150/95	2	16
V. F.	42	4	12	0.20	151	136	128	215/120	190/110	175/105	1	17
T. P.	61	3	12	0.10	146	138	110	200/120	185/115	140/95	1	17
I. C.	51	3	14	0.10	160	140	106	220/130	190/115	140/90	1	16
J. S.	57	3	10	0.10	145	123	111	195/120	170/100	145/95	2	15
L. B.	50	4	12	0.20	163	126	114	250/120	190/95	175/90	3	13
L. W.	52	4	12	0.10	183	137	113	270/140	210/100	160/90	1	5
Cryptenamine-reserpine			11	0.175	158	134	113	224/125	188/107	153/93	1.7	14
All patients on cryptenamine alone			12.2		153	121		217/122	163/97			

*Mean blood pressure equals diastolic plus one-third of the pulse pressure.

combinations for periods as long as two years.

Methods and Materials

Forty-one office patients comprised the study group. Thirty-three were men, eight, women. All were considered to be suffering from primary ("essential") hypertension, and ranged in age from 35 to 79 years with a mean of 59 years. Two patients fell into Grade 2, 23 into Grade 3, and 16 into Grade 4 of the conventional Smithwick classification.[20] The known mean duration of hypertension was $6^1/_2$ years with extremes of less than one and more than 20 years. Baseline observations were available for an average of more than 14 months for the entire group. Previous therapy had encompassed restricted sodium diets in all, and most had received courses of barbiturates, with and without theobromine. Many had been treated with Hydralazine®, ganglionic "blocking" agents, and Dibenzyline®, often in combination, without success. Prior to initiation of cryptenamine treatment, all patients but one exhibited diastolic blood pressures repeatedly at or above 110 mm Hg. Nine patients had suffered cerebrovascular accidents, four had been treated for cardiac infarctions, and ten were in varying stages of congestive heart failure. Azotemia was present in 17 patients.

Initial and serial studies included history and physical examination, funduscopic evaluation, urinalysis, hemogram and sedimentation rate, electrocardiogram, roentgenograms and fluoroscopy of the chest, estimation of blood urea nitrogen and phenolsulfonphthalein excretion. All patients were seen weekly during the early months of treatment. Blood pressure and pulse rates were recorded in the seated position.

Treatment consisted of continuation of the reduced sodium intake and adjunctive measures previously received. All patients were started on cryptenamine alone at first, utilizing 2 mg tablets.* Treatment was begun with one tablet immediately after breakfast, one tablet at 2 p.m., and one tablet at bedtime. The daily dose was increased by one or two tablets every seven days in stepwise fashion, and the final total adjusted so that the medium dose was taken after breakfast, the minimum dose in mid-afternoon, and the maximum dose upon retiring. All patients were instructed to refrain from eating for at least four hours after each dose in an attempt to minimize possible reactions.

* Made available as Unitensen® by Thomas A. Garrett, M.D., Medical Director, and B. A. Marty, Director of Clinical Research, Irwin, Neisler & Co., Decatur, Illinois.

Results

Physiologic response (table 1)

(A) *Cryptenamine Alone:* All 41 patients received cryptenamine as initial therapy. This group exhibited a decrease in average mean blood pressure from 153 mm Hg (217/122) to 121 mm Hg (163/97). The final daily maintenance dose of cryptenamine ranged from 8 to 16 mg and averaged 12.2 mg. Twenty-four patients continued on cryptenamine as sole medication during the entire period of study. The average control mean blood pressure for this group was 155 mm Hg (212/127) and fell to 120 mm Hg (156/103). The daily maintenance dose ranged from 8 to 16 mg and averaged 13 mg. Cryptenamine requirements remained relatively stable once the daily ration dose for each patient was determined. In six patients the final maintenance dose was less, in one patient it was more, and in 17 patients it remained constant throughout the period of observation, differences being chiefly in the range of one or two tablets (2 to 4 mg) daily.

(B) *Cryptenamine Plus Rauwolfia:* Seventeen patients were treated first with cryptenamine and then reserpine was added, in dosage of 1 mg daily, the latter administered as a single daily ration. The control mean blood pressure of 158 mm of Hg (224/125) of this group declined to 134 mm Hg (188/107) when cryptenamine was given, and to 113 mm Hg (153/93) on combined cryptenamine-reserpine medication. The treatment program for these patients made it possible to compare the daily requirement of cryptenamine before and after the addition of reserpine. The average daily dose of cryptenamine when used alone was 12.4 mg; after addition of reserpine the daily requirement of cryptenamine was 11.0 mg. The final maintenance dose of reserpine ranged from 0.1 mg to 0.5 mg,

and averaged 0.175 mg daily for the entire group.

CLINICAL RESPONSE

Institution of cryptenamine and cryptenamine-reserpine treatment was marked by alleviation of headache, lessening of palpitation, decrease in the frequency and severity of angina and relief of dyspnea, in descending order of frequency (Table II). In several patients overt congestive heart failure abated coincident with the depressor response and digitalization was not necessary; in others, frank clearing of the signs of failure did not occur despite conventional management until the elevated blood pressure was reduced.

TABLE II

The Course of Symptoms in Forty-One Patients with Arterial Hypertension Following Treatment with Cryptenamine and Cryptenamine plus Reserpine

Symptom	Number*	Improved	Same	Worse	Improved, %
Headache	27	21	5	1	77.7
Angina	15	9	3	3	60.0
Exertional dyspnea	17	8	7	2	47.0
Palpitation	20	13	7	0	65.0

* Expressed as the number of patients complaining of the particular symptom.

Laboratory Data: Initial baseline studies were repeated serially in all patients (Table III). In addition to the recorded sphygmomanometric changes, cardiomegaly regressed and funduscopic findings improved in a substantial proportion of those treated. Alterations in the electrocardiogram, regression of proteinuria and lessening of the degree of nitrogen retention were less regularly observed.

Side Reactions: No side effects were reported by 28 of 41 patients treated only with cryptenamine. In the remainder, gastrointestinal symptoms and circumoral paresthesias were noteworthy. Emesis, which could be clearly related to therapy, occurred in the course of treatment of one patient. The majority of those who experienced side reactions to cryptenamine alone received combined therapy as the final mode of management. No side effects were reported by 58 per cent of this latter group. Symptoms in the remainder consisted principally of nasal stuffiness, diarrhea, nightmares, lightheadedness, and what we have termed the "heat reaction," i.e., a profound depressor response below treatment levels during periods of high environmental temperature and humidity. Side reactions to therapy are summarized below:

(A) *To Cryptenamine Alone* (all 41 patients)	
(1) No side effects	28 (68.2 per cent)
(2) Side effects	13 (31.8 per cent)
(a) Nausea alone	6
(b) Nausea and emesis	1
(c) Diarrhea	2
(d) Eructation	1
(e) Bitter taste	2
(f) Perioral paresthesias	1
(B) *To Cryptenamine Plus Reserpine* (17 patients)	
(1) No side effects	10 (58.8 per cent)
(2) Side effects	7 (41.2 per cent)
(a) Heat reaction	4
(b) Lightheadedness	1
(c) Nasal stuffiness	3
(d) Diarrhea	1
(e) Nightmares	1

TABLE III

Objective Changes in the Course of Forty-One Patients with Arterial Hypertension Following Treatment with Cryptenamine or Cryptenamine plus Reserpine

Clinical Sign	Number*	Improved	Same	Worse	Improved %
Funduscopic changes	41	24	13	4	58.5
Enlarged heart	20	13	6	1	65.0
Abnormal ECG	37	10	25	2	27.0
Proteinuria	31	12	19	0	38.7
Nitrogen retention	17	6	5	6	35.2

* Expressed as the number of patients exhibiting the abnormal manifestation recorded.

Discussion

The past decade has witnessed the evolution of new concepts in the treatment of the patient suffering from abnormal elevation of the arterial blood pressure. Heretofore any approach to this problem was conditioned by reference to the prolonged, uncertain, and variable course of the disease, and the fear that the induction of hypotension might compromise blood flow through organically altered vascular beds.[21] An accumulated experience with many new chemotherapeutic agents has documented the feasibility of obtaining significant decrements in abnormally elevated blood pressure readings.[22–25] Concern as to possible harmful effects in vital areas has given place to the realization of the dividends of reduced demand on the body as a whole, reversal or delay of complicating conditions, and prolongation of life in more severe forms of the disease.[26] In less severe degrees of hypertensive illness, "prolonged, continuous and adequate therapy is apparently associated with a change in the basic process producing hypertension,"[27] in many instances, permitting withdrawal of all therapy with subsequent persistence of normotension. In the opinion of students of the disease, an attempt at lowering the abnormally elevated blood pressure is considered justified in most hypertensive individuals.[24,26]

At the same time that new hypotensive agents have been introduced, older, previously discarded drugs, of which veratrum was one, have been re-examined critically. The pharmacology of the veratrum alkaloids has recently received authoritative review,[28] to which the interested reader is referred. Veratrum-induced hypotension is mediated both by reflex vagal stimulation and central vasodepression. The principle mechanism is sensitization of afferent vagal nerve endings in the left ventricle and great vessel walls, and to a lesser degree in the lungs—the "Bezold Effect." Hypotension results from widespread reflex vasodilatation; sinus bradycardia accompanies the fall in blood pressure and may be dissociated from the latter by atropinization. A direct effect of these alkaloids on blood vessel walls has not been demonstrated. Adrenergic or ganglionic blockade does not result from their action.

The usefulness of vertrum is inherent in these properties which include many of the requisites of the "ideal" hypotensive agent. Therapeutic amounts do not induce tachycardia, a decrease in cardiac output or venous pooling with resultant postural hypotension. Because of the absence of ganglionic blockade normal vasomotor lability and reflexes are not altered. The renal vasculature participates in the reflex vasodilatation;[29] cerebral blood flow and oxygen utilization are preserved or augmented, while cerebrovascular resistance falls.[30,31]

Early use of veratrum in the treatment of arterial hypertension was limited by the availability of crude extracts only, containing mixtures of the component alkaloids in uncertain proportions requiring biologic standardization. Gastrointestinal symptoms, of which nausea and emesis were the most disturbing, occurred regularly with dosages virtually identical with those inducing a drop in blood pressure. Later, single purified alkaloids offered the promise of weight standardization and more critical adjustment of dosage, but it was still not possible to employ consistent ration doses capable of lowering the blood pressure without producing emesis with great frequency.[32–39]

Studies dealing with the parenteral use of cryptenamine in laboratory animals,[16] and later in the treatment of hospitalized patients,[40] were provocative of interest in its possible value for office or outclinic management of patients with high blood pressure. Our findings in a "pilot" group of patients refractory to other antihypertensive therapy suggested that oral cryptenamine was a safe and moderately effective hypotensive agent when given as sole treatment, and that side reactions were mild and transitory. Emesis was decidedly infrequent in the course of these patients. The wider therapeutic index of cryptenamine as compared with other veratrum alkaloids has received comment elsewhere.[25,41,42] The synergistic action of cryptenamine and rauwolfia derivatives acting in concert was further demonstrated by Herren and associates[43] in a study in which three-quarters of the patients treated with this combination achieved a "satisfactory response."

The data presented suggest that oral cryptenamine has value in the long-term treatment of

moderately severe hypertensive illness. Patient co-operation was of a high order and office management was possible in all instances. Progress of patients under therapy was guided by the use of conventional diagnostic equipment and routine clinical laboratory procedures. Therapy was titrated to individual requirements by stepwise adjustment of dosage.

On this basis, oral cryptenamine appeared to be a safe and moderately potent antihypertensive preparation. Twenty-four of 41 patients observed obtained substantial blood pressure reduction when taking this drug alone. Once a cryptenamine-induced blood pressure "floor" was reached, three dose-response patterns developed. Almost three-quarters of the patients needed no further revision of dosage, corroborating the constancy of daily ration doses and lack of development of tolerance to veratrum remarked by others.[4,44] One-quarter of those treated, on the other hand, demonstrated increased reactivity to the same daily amount of cryptenamine; the blood pressure decrement originally induced could then be maintained with smaller ration doses as treatment continued, an experience resembling that of Wilkins with oral Veriloid®,[45] and Corcoran *et al.*[37] with protoveratrine. One patient demonstrated a gradual rise in pressure following an initially successful cryptenamine titration, presumably the clinical counterpart[9] of the tachyphylaxis of animal studies.[46]

When reserpine, a rauwolfia alkaloid, was added to the basic cryptenamine therapy of 17 patients who demonstrated a suboptimal depressor response, a further drop in blood pressure followed. The use of combined therapy made possible a reduction in total cryptenamine ration averaging 1.4 mg daily.

Side effects were noted by somewhat less than one-third of the entire group while receiving cryptenamine alone. Gastrointestinal symptoms were chief among these, with nausea the most frequently reported feature. Emesis, which could be related clearly to therapy and not to intercurrent illness or dietary indiscretion, occurred in one patient on several occasions. Three-fifths of those whose final treatment comprised cryptenamine-reserpine combinations were free of side reactions. Of the two-fifths who noted symptoms on combined therapy, the most prominent effect was a profound depressor response during periods of high environmental heat and humidity. This was attributed to excessive salt loss in the sweat, and, as our experience developed with this program, patients were instructed to increase their dietary salt intake at such times. We have not, accordingly, encountered this response during the last year of observation. Similar phenomena have been noted with other potent hypotensive medications and are not considered peculiar to the particular substances herein described. Nasal congestion was also of modest frequency among the side effects from combined treatment and was considered to be a characteristic expression of rauwolfia. None of the foregoing limited treatment which could be continued without interruption while dosage was revised or the daily mealtime routine adjusted.[12,25]

The decrease in typical "hypertensive headache," alleviation of angina and palpitations, as well as regression of signs and symptoms of loss of cardiac reserve, suggest that cryptenamine alone or combined with reserpine was helpful in many instances. Many patients remarked spontaneously upon a general feeling of well being, particularly those with the most pronounced hypotensive response. It is further noteworthy that no patient who remained on therapy for the entire period of observation experienced myocardial infarction or a cerebrovascular accident or developed clinical uremia, although these complications had marked the prior course of this group. Serial laboratory studies documented improvement chiefly in heart size and ophthalmoscopic findings, while effects in the renal area and on the electrocardiogram were less consistent.

Although the limited number of patients studied precludes valid statistical evaluation which would permit accurate preselection of patients for cryptenamine therapy, the data presented would indicate that the individual most likely to benefit is the hypertensive with involvement chiefly in the cardiac and retinal areas and with relatively intact renal function. Patients with serious compromise of renal reserve seemed less susceptible to cryptenamine, although the improvement in renal hemody-

namics attendant upon veratrum therapy[29] might theoretically be expected to be salutory in those less severely afflicted.

The evidence to date suggests that individuals who are candidates for cryptenamine therapy should receive a rauwolfia preparation alone for at least three weeks.[47] If a decided depressor effect ensues, this drug is continued until its maximal exhibition and cryptenamine is then begun. If only a modest decrement or little change in blood pressure occurs with rauwolfia alone, cryptenamine is immediately added in stepwise fashion as indicated in the section on Materials and Methods. Rauwolfia "priming" enhances the hypotensive potency of cryptenamine and may be expected to prevent or ameliorate side reactions to the latter. After an optimal response to combined therapy is obtained the patient should be maintained on both drugs for at least six months, following which one may attempt revision of one or both dosages downward. Finally, it may be possible to withdraw the more potent cryptenamine without sacrifice of blood pressure control.[27,47] We prefer to administer cryptenamine and reserpine separately during the early stages of titration because of the wider latitude possible in altering dosages at any time. The recent development of combination tablets* incorporating both hypotensive agents has made it possible to substitute a more convenient single preparation when the requirements of individual patients have stabilized.

Summary

(1) Cryptenamine (unitensen), an alkaloid of veratrum viride, was administered to 41 office patients with arterial hypertension of moderate severity for periods up to two years, by the oral route. The daily cryptenamine dose was distributed so that the medium dose was taken after breakfast, the minimum dose at 2 p.m., and the maximum dose at bedtime.

(2) Oral cryptenamine appeared to be a moderately potent antihypertensive agent when used as the sole mode of therapy on a long term basis. Sixty-eight per cent of the patients so treated reported no side reactions; in the remainder, gastrointestinal symptoms were mild and transitory. Emesis, previously reported as infrequent with cryptenamine therapy, occurred in one patient and was not a limiting factor in continuing treatment.

(3) The addition of reserpine, a rauwolfia alkaloid, to the basic cryptenamine therapy of 17 patients enhanced the depressor response to the latter and ameliorated side effects. In this group receiving combination therapy the most notable side-effect was a syndrome attributed to excessive loss of salt in the sweat during periods of high environmental heat and humidity.

(4) These data suggest that cryptenamine, alone or with reserpine, has value in the office management of the patient with arterial hypertension over prolonged periods. Clinical and laboratory observations appear to indicate that this therapy may be most effective in the hypertensive individual with cardiac and retinal area involvement and with relatively intact renal function.

* Unitensen tablets containing 1 mg of cryptenamine and 0.1 mg of reserpine are commercially available. During the later therapy of our patients a new combination tablet containing 2 mg of cryptenamine and 0.08 mg of reserpine was made available by Thomas A. Garrett, M.D., Medical Director, Irwin, Neisler & Co. and this permitted more critical approximation of doses of these agents when they are given individually.

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Case Reports

Rupture of Aortic Aneurysm Into Left Pulmonary Artery*

Attempt at Surgical Correction

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APPROXIMATELY 90 cases of rupture of a syphilitic aneurysm of the aorta into the pulmonary artery have been published or reviewed since the clinical entity was first described in 1839.[1] Although relatively rare in the course of luetic heart disease, this usually disastrous event has come to be associated with a definite syndrome and an antemortem diagnosis can often be made on the basis of clinical findings alone. This was first reported as early as 1861.[1] However, cardiac catheterization and angiocardiography provide confirmatory data. Seven of the nine cases[2–8] reported since the last complete review by Nicholson[1] in 1943 were clinically diagnosed, and five were confirmed by cardiac catheterization.

This type of vascular accident is often rapidly fatal and no active therapy could be offered until recently. However, since the surgical repair and reconstruction of diseased great vessels has become an actuality, a new approach to this problem is possible. To date, only one case has been reported in which an attempt at surgical repair was made.[8] The purpose of this paper is to present another such case.

CASE HISTORY

W. G. (#69047), a 52-year-old Negro male porter, was admitted to Montefiore Hospital on October 4, 1954 for evaluation of his cardiac status. He had been well until October, 1953 when, performing his usual duties as a porter, he had a sudden onset of pain in the left anterior chest and left arm. At the same time he noted shortness of breath and headache. He consulted a physician and was treated with a low-salt diet, mercurial injections and digitalis for two weeks without improvement. During this period he had increasing orthopnea and paroxysmal nocturnal dyspnea, and was hospitalized elsewhere on November 10, 1953. At that time he had a blood pressure of 130/30, an enlarged heart, and loud systolic and diastolic murmurs heard best in the third left anterior intercostal space. An electrocardiogram was reportedly normal. A chest x-ray revealed generalized enlargement of the heart with a prominent bulge of the pulmonary artery segment. Serologic test for syphilis was positive. The sedimentation rate was elevated and his temperature rose to 101° F. Other laboratory procedures included normal blood urea nitrogen, fasting blood sugar, blood count and urinalysis. The dosage of digitalis and nitroglycerin was increased and there was some improvement. After two weeks he was discharged to a clinic with the diagnosis of luetic aortic insufficiency and possible rheumatic heart disease.

Despite continued therapy with digitalis and intermittent mercurial injections, congestive failure recurred and he became severely orthopneic and dyspneic. On April 9, 1954 he was again hospitalized and received more intensive therapy for congestive heart failure as well as a course of penicillin for syphilis. However, after discharge, congestive heart failure again increased and he was readmitted for a third time on September 4, 1954. At that time his heart was greatly enlarged to the left and right and there was marked accentuation of the pulmonary artery segment on x-ray. No enlargement of the left auricle could be demonstrated. He was trans-

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ferred to Montefiore Hospital on October 4, 1954 for further evaluation and therapy.

Past history included gonorrhea at the age of 18, but no history suggestive of rheumatic fever. Pertinent physical findings included: Weight—60.6 kg; blood pressure in the right arm 124/44/0, left arm 136/46/30, right leg 240/80/0, left leg 220/80/0. There were bilateral arcus senilis, and minimal nicking and arteriolar narrowing on funduscopic examination. No tracheal tug was found, but carotid pulsations were exaggerated and the neck veins were distended, with a positive hepatojugular reflux. Rales were heard at the left lung base. The heart was enlarged, with the point of maximum impulse in the 5th left anterior intercostal space at the anterior axillary line. A harsh systolic murmur was heard best in the 2nd and 3rd left anterior intercostal spaces, and a softer blowing systolic murmur was present at the apex. A blowing diastolic murmur was also heard on both sides of the sternum in the second and third interspaces anteriorly. There were no thrills. The heart rate was 76, without pulse deficit, and there were occasional premature ventricular contractions. The pulmonic second sound was louder than the aortic second sound. A soft, tender liver edge was palpable 4 fingers' breadth below the costal margin. Shifting dullness was present in the abdomen. There was no clubbing or cyanosis. All peripheral pulses were present and Corrigan pulse, Duroziez's sign and Quincke's pulsations were noted.

The hemoglobin ranged between 11.5 and 13 g % and white blood cell counts varied from 2,400 to 4,800 with normal differential counts. Urine specimens repeatedly contained 3–4 plus albumin with specific gravities varying from 1.010 to 1.025 on casual specimens. Bleeding, clotting and prothrombin times, as well as platelet counts, were normal. Clot retraction was good. The sedimentation rate by the Cutler method was 22 mm/hr. The blood urea nitrogen was 26.2 mg %. Serum electrolytes were as follows: CO_2 29.1 meq/*l*, chlorides 98.4 meq/*l*, sodium 133 meq/*l* and potassium 4.8 meq/*l*. Fasting blood sugar was normal. The alkaline phosphatase was 13.8 Bodansky units and bromsulphthalein retention was 21 per cent in 45 min. Other liver function tests were normal. Two blood cultures were sterile. The VDRL and Kolmer tests of the blood were 4 plus positive. Examination of the spinal fluid revealed an initial pressure of 420 mm of water, 22 mg % protein and positive tests for syphilis. Final pressure was 240 mm of water.

The electrocardiogram revealed clockwise rotation, left axis deviation and premature nodal and ventricular beats with periods of bigeminy. There was also a large R wave in lead aVR and a smaller R in V_1 which were interpreted as evidence of right ventricular enlargement (Fig. 1). Fluoroscopy revealed a markedly prominent pulmonary artery segment and increased hilar vessels without intrinsic pulsations. There was considerable enlargement of outflow and inflow tracts of the left ventricle, and of inflow tract of the right ventricle. Both auricles were normal. Calcification was noted and

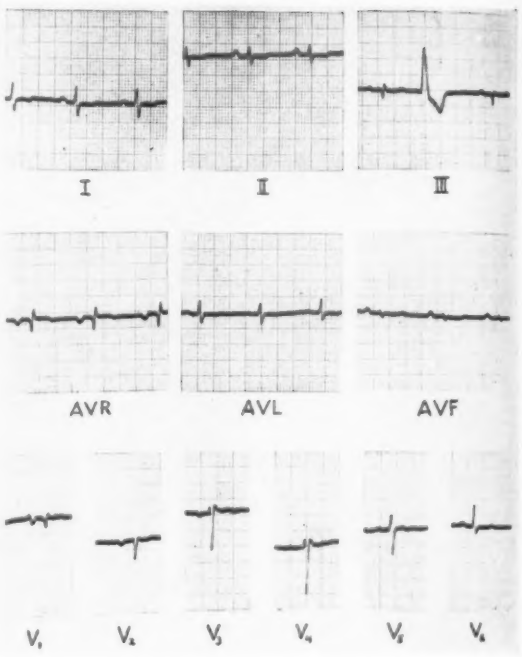


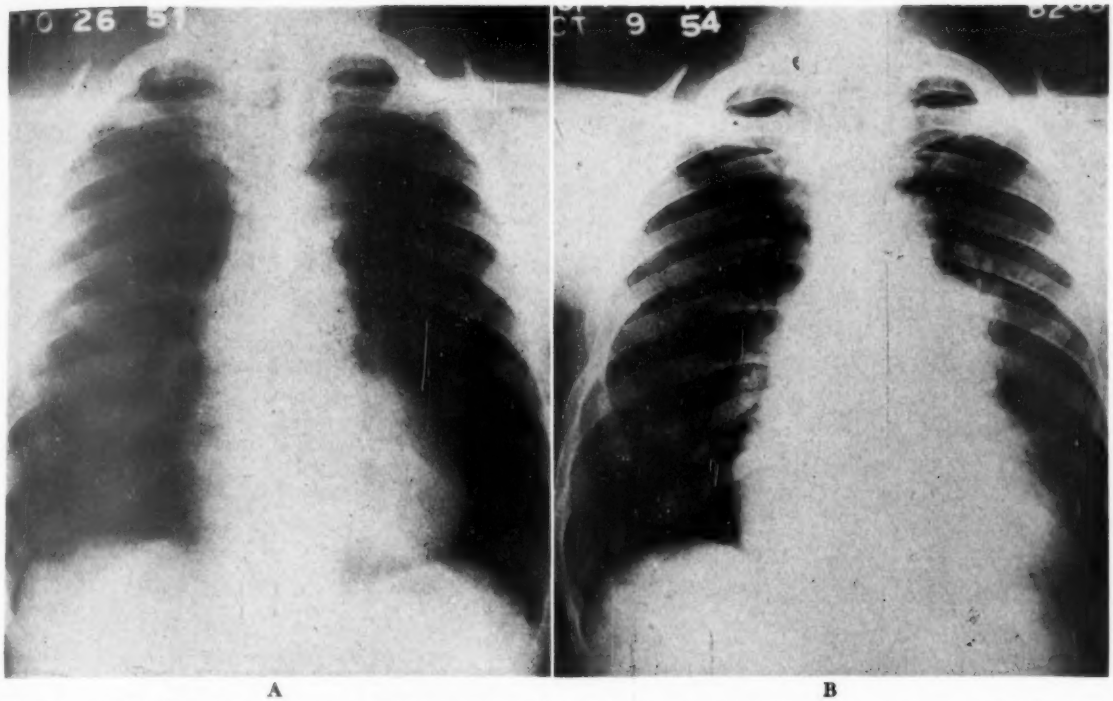
Fig. 1. Electrocardiogram.

TABLE I
Cardiac Catheterization
(October 18, 1954)

Location of sample	Oxygen content %	Pressure	
		Systolic/diastolic	Mean
Pulmonary "wedge"		18/13	(14)
Pulmonary artery, main	69	73/16	(31)
Pulmonary artery, left	82	75/45	(55)
Right ventricle, near tricuspid	49	73/0-10	(21)
Right atrium	51	17/12	(15)
Superior vena cava	62		
Inferior vena cava	51		

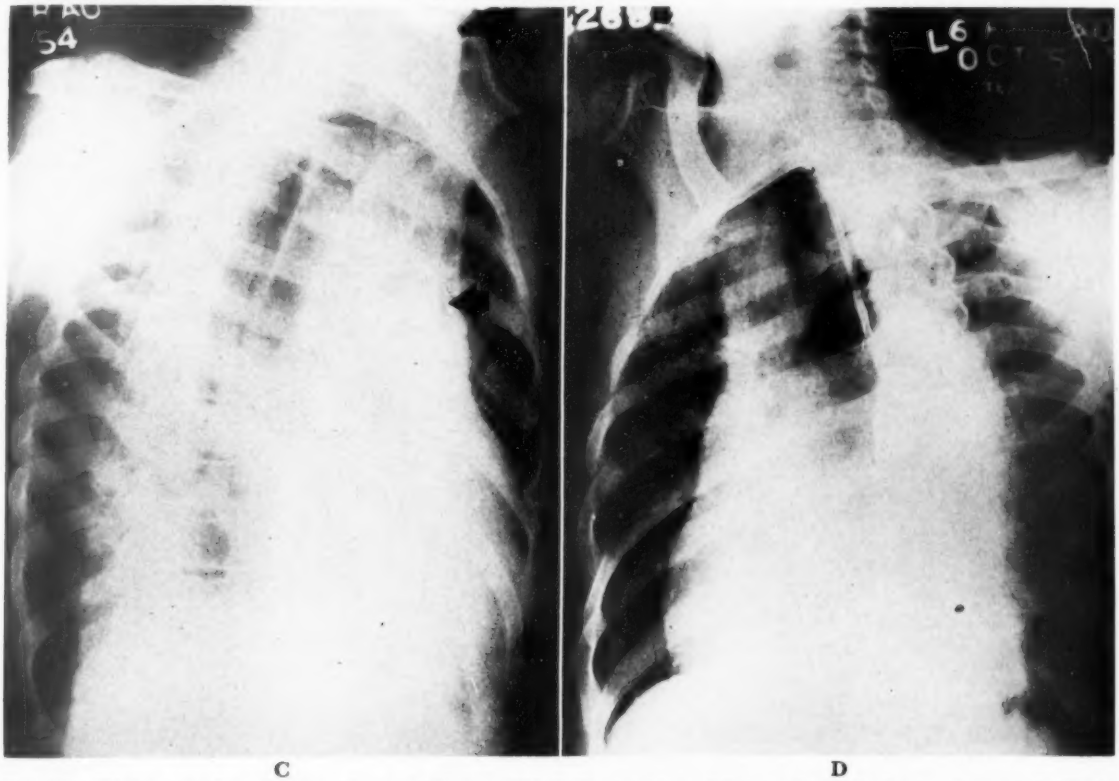
believed to be in the pulmonary artery. Chest x-rays confirmed the findings except that the calcification was localized in the ascending aorta rather than the pulmonary artery (Fig. 2). Also noted were prominent left pulmonary vascular markings. A routine photofluorogram taken in 1951 was subsequently obtained and is shown for comparison (Fig. 2, A,B,C,D). The decholin circulation time was 55 sec and the venous pressure was 140 mm of water.

The patient was afebrile throughout his hospital course. Therapy for congestive heart failure included low-salt diet, aminophyllin, mercurial injections and



A B

Fig. 2A. 1951 photoroentgenogram of chest presumably taken prior to rupture of aneurysm. (B) Postero-anterior chest roentgenogram taken during final illness.



C D

Fig. 2C. Right anterior oblique view of chest. (D) Left anterior oblique view of chest. Arrows indicate calcification in wall of aneurysm.

Fig. 3. Retrograde aortogram. Aneurysmal dilatation of ascending aorta, saccular aneurysm, flow into pulmonary circulation, and reflux into left ventricle are demonstrated.

daily digoxin. He responded well, with a 7.6 kg weight loss, and became asymptomatic. Although the edema subsided, the liver remained enlarged, but was no longer tender. A diagnosis of possible acquired aortic-pulmonary artery fistula was made and cardiac catheterization was performed on October 20, 1954 (Table I). The results indicated a left-to-right shunt into the left pulmonary artery. On October 27, 1954 a retrograde aortogram was done via the left femoral artery (Fig. 3). This revealed an aneurysmal dilatation of the ascending aorta and proximal portion of the aortic arch, and a prominent posterior daughter aneurysm which communicated with the pulmonary circulation. Insufficiency of the aortic valve was indicated by the appearance of contrast medium in the left ventricle.

That evening the character of the murmurs changed; they now had a continuous machinery-like quality, and were best heard in the third left anterior intercostal space, with radiation to the left posterior chest. The clinical course, however, had not changed. The patient was presented at the Montefiore Cardiovascular Surgical Conference[11] on November 2, 1954 and it was decided that surgical obliteration of the shunt with repair of the major vessels would be attempted after another course of antiluetic therapy.

Surgical Findings and Results: On November 30, 1954 an attempt at surgical repair was made (E.S.H.). Under satisfactory general intratracheal anesthesia, the patient was refrigerated in an ice tub to 90°, before being placed in the supine position on the operating table, with about 10° of elevation of the left thorax. An anterior transthoracic incision was made overlying the level of the third interspace in the midline, and skirting below both nipples. The left and right pleural cavities were widely entered through the 3rd interspaces, and the sternum

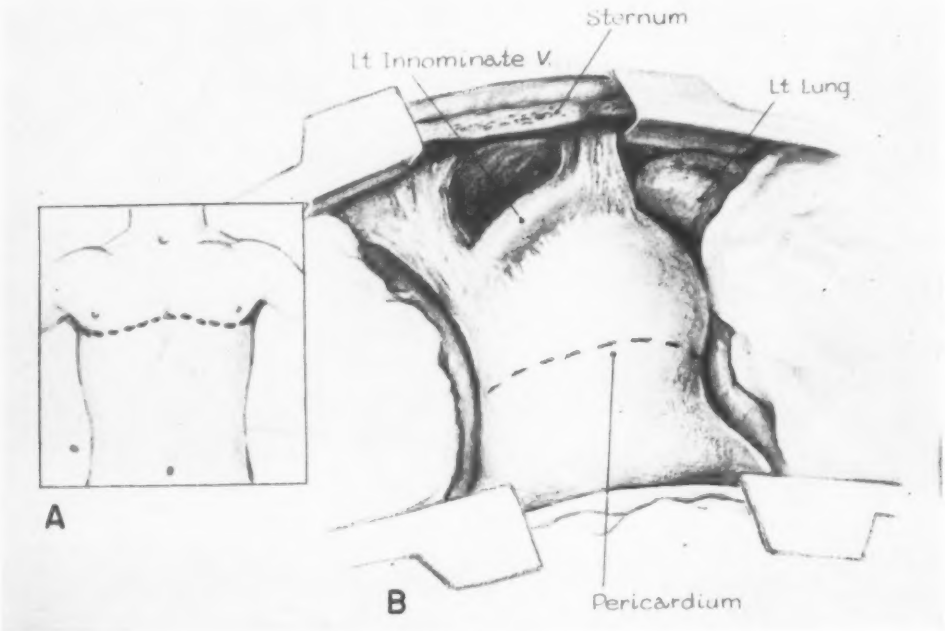


Fig. 4. Incision and exposure.

divided transversely with a Gigli saw. A large aneurysmal mass occupied the entire midportion of the operative field, and the heart was displaced inferiorly. (Fig. 4.) The pericardium was widely opened in a rectangular flap that extended vertically along the right phrenic nerve, with horizontal extensions superior and inferior to the aneurysm, extending almost to the left phrenic nerve inferiorly. Superiorly the pericardium was adherent to a portion of the aneurysmal mass. A plane of cleavage was identified just above the base of the heart, in the sulcus between the origin of the pulmonary artery medially, and the origin of the aorta laterally. The transverse sinus was free, and a finger could be passed completely behind both the aorta and pulmonary artery (Fig. 5). The aorta seemed to be approximately normal

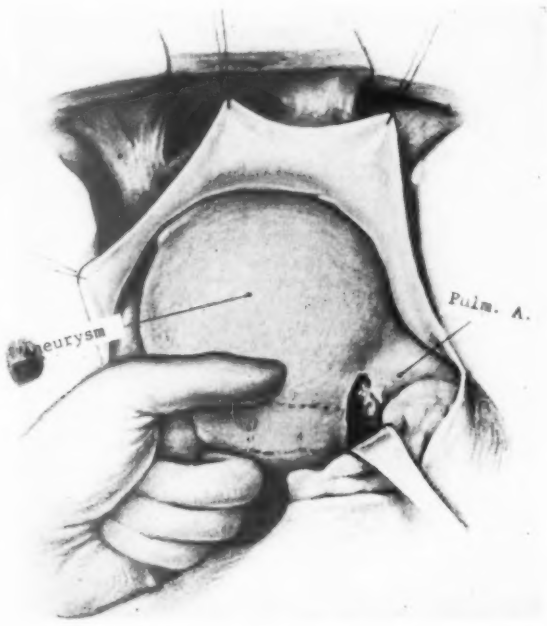


Fig. 5. Pericardium opened and base of aorta mobilized from pulmonary artery; finger in transverse sinus.

in size at its origin, and then ballooned out in a fusiform dilatation which presented a saccular component about the size of a tennis ball occupying the space between the aorta and pulmonary artery. If there was a neck to this sacular aneurysm, the superior margin of this was never delineated at operation. The inferior margin was dissected by careful mobilization in the plane between the aorta and pulmonary artery. In the course of this mobilization, the pulmonary conus was retracted medially. At this point, it was noted that the heart rate became extremely slow, beats became ectopic, and ventricular fibrillation developed. The body temperature had dropped to between 84 and 85° at this time. After almost three hours of attempted resuscitation, the patient was pronounced dead.

Autopsy Findings: On postmortem examination,* pertinent findings were restricted to the chest except for minimal centrilobular liver congestion. There was an approximately 30 cm long anterior sternum splitting incision across the chest. The pericardium showed the surgical incision. The heart weighed 750 g. All cardiac chambers were dilated and hypertrophied, especially the right and left ventricles which measured 0.5 and 1.5 cm, respectively. The aortic and pulmonary valve rings were significantly widened and measured 10 cm in circumference. The leaflets of the tricuspid and pulmonic valves were not remarkable. There was very slight thickening of the free edges of the mitral leaflets with normal chordae tendineae. The aortic valve cusps showed an insignificant amount of fusion at the posterior commissure and minimal thickening around the corpora Arantii. The remainder of the cusps was thin and translucent. Below the posterior commissure the left ventricular endocardium was minimally thickened but the endocardial surfaces elsewhere were normal (Fig. 6). The coronary ostia were patent and the coronary arteries showed minimal atherosclerosis. Except for the hypertrophy there was no myocardial lesion.

The first portion of the aorta was markedly dilated in a fusiform manner, reaching about four times the normal diameter at the ascending portion of the arch. This dilatation extended to the middle of the transverse portion of the arch. On the anteromedial border of the fusiform enlargement of the arch there was a saccular evagination with a neck measuring 6 cm in diameter. This sack was about 8 cm across at its widest part. It extended anteromedially to cover the anterior aspect of the main pulmonary artery. The wall of this saccular aneurysm measured 1.5 mm in thickness. The intima of the thoracic aorta was markedly atherosclerotic, with some ulceration and calcification in addition to linear longitudinal scars of luetic aortitis. The extreme left lateral wall of the saccular aneurysm was fused with the walls of the main and left pulmonary arteries. A 1 cm slit-like communication connected the lumina. This fistula was located 1 cm beyond the origin of the left pulmonary artery on its anterosuperior surface. It was well endothelialized (Fig. 7).

Each pleural cavity contained about 200 cc of bloody fluid. Both lungs were atelectatic. The right lung weighed 525 g, the left lung 500 g. The cut surfaces of both sides revealed congested, atelectatic and red parenchyma. A moderate amount of frothy pink fluid could be expressed from the cut surfaces of all lobes. The tracheobronchial tree contained a moderate amount of extremely viscid mucoid material.

Microscopic examination confirmed the gross impression of luetic aortitis with aneurysmal dilatation and sac-formation in the ascending portion of the arch of the aorta with communication into the left pulmonary artery.

* Autopsy was performed by Leon Gordon, M.D., of the Laboratory Division.

Discussion

The syndrome of rupture of an aneurysm of the ascending thoracic aorta into the pulmonary artery has been adequately described.[1,10] A sudden onset of severe precordial or substernal pain which may or may not radiate to the left

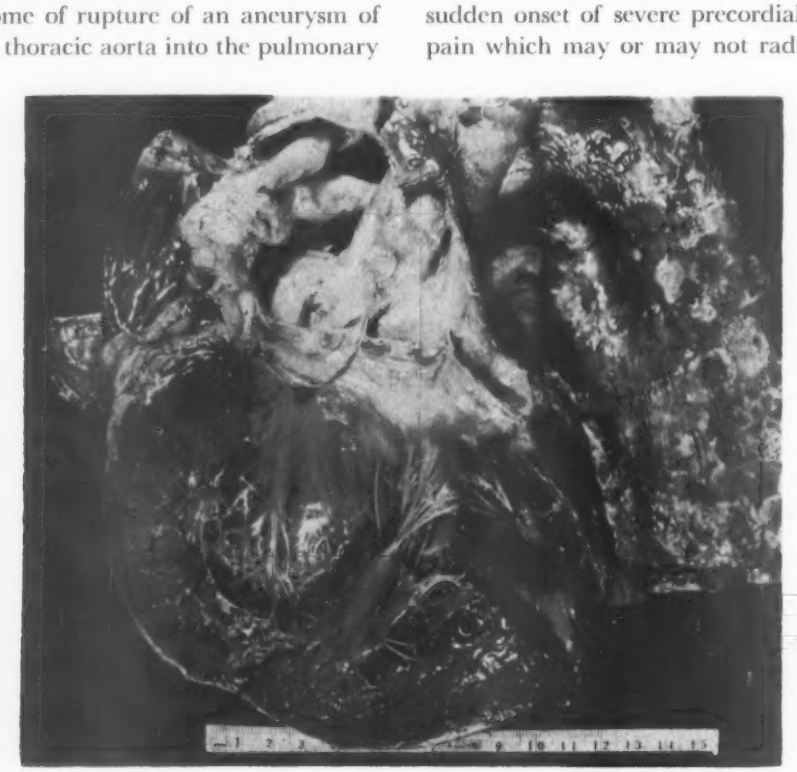


Fig. 6. Postmortem photograph of heart and aorta. Left ventricular hypertrophy, aneurysmal dilatation of the aorta and changes in endothelial lining are evident.

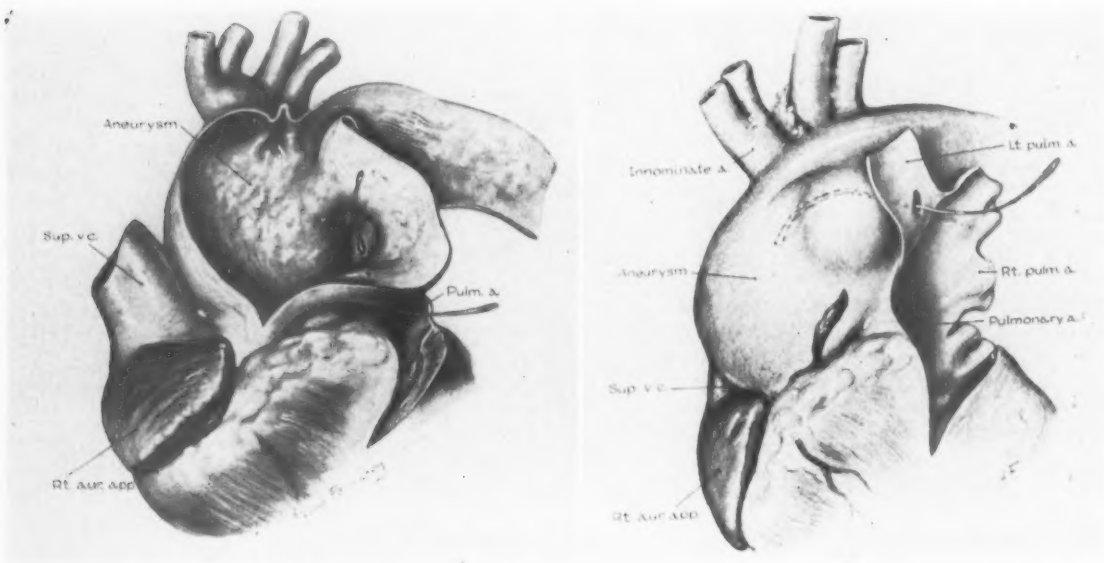


Fig. 7. Postmortem drawing of aneurysm and perforation from (A) aortic aspect and (B) pulmonary artery approach.

arm, or of shortness of breath, is typically followed by the rapid development of severe right-sided cardiac decompensation. A continuous machinery-type murmur or separate systolic and diastolic murmurs and associated thrills in the 2nd and 3rd intercostal spaces to the left of the sternum and peripheral signs of aortic valvular incompetence are usually present. An aneurysm of the aorta and possibly a prominent pulmonary artery may be demonstrated on x-ray examination, while the ECG will often show right axis deviation or right ventricular hypertrophy despite the presence of the large left ventricle. The serologic test for syphilis is most often positive. The clinical course is usually rapidly downhill. The duration of life following the onset may be brief. Although survival up to four years has been reported, few cases have survived more than six months.

Postmortem examination in this case revealed compression of the pulmonary artery by the aortic aneurysm. This effect is generally considered sufficient to cause an increase in pulmonary artery pressure and resistance, and to throw an excessive load on the right ventricle.[9] In addition, the sudden shunting of blood into the lesser circulation may augment this effect and account for the frequent ECG findings of right ventricular preponderance.

The site of rupture of an aneurysm of the ascending aorta into the pulmonary circulation is most often the main pulmonary artery.[1] Rupture into the left pulmonary artery was suspected in this case from the appearance of the chest x-ray in which the left lung field showed greater vascularity than the right. This location of the fistula was then confirmed by cardiac catheterization.

Differential Diagnosis: Lesions associated with continuous machinery or separate systolic and diastolic murmurs in the 2nd and 3rd interspaces to the left of the sternum must be considered.[12] Although patients with uncomplicated luetic aortic insufficiency may have a similar clinical course, the presence of a large left ventricle and right axis deviation on ECG should suggest the possibility of an aortopulmonary artery fistula. Cardiac catheterization and aortography should be carried out in these cases in an attempt to confirm the presence of the abnormal communication. These methods also may establish the location and size of the abnormal communication. The feasibility of surgery as well as the surgical approach are determined on the basis of such data. However, only by thoracotomy can actual operability be determined.

The continuous murmur associated with persistent patent ductus arteriosus is best heard in the second left intercostal space and is transmitted laterally below the clavicle.[12] While peripheral signs of aortic insufficiency may be present, an uncomplicated patent ductus arteriosus is associated with a normal electrical axis or left axis deviation.

Rupture of an aneurysm of the aorta into the superior vena cava produces a continuous murmur that is usually heard to the right rather than the left of the sternum.[13] An aneurysm of the sinus of Valsalva may rupture into the right auricle, right ventricle, or pulmonary artery and produce a similar clinical picture. The murmur may have a more superficial quality and be localized at the 3rd or 4th left interspace.[14,15] Other lesions, such as an interventricular septal defect with or without associated aortic valvular deformities, anomalies of the pulmonary and coronary vessels, and congenital or traumatic fistulae may also be present with continuous murmurs. However, the clinical course and other appropriate studies will differentiate these conditions.

Surgical Treatment: The site of the fistula, between the aorta and the left main pulmonary artery, had been accurately localized preoperatively in the present case. Hypothermia was employed to provide protection against anoxia of the spinal cord and kidneys in case temporary occlusion of the aorta became necessary. The assumption, however, that one might be able to find a plane of cleavage between the aortic aneurysm and the pulmonary artery, and proceed with closure of the fistula, was entirely erroneous. Had this operation not been terminated by the advent of irreversible ventricular fibrillation, and the contemplated dissection continued, hemorrhage would undoubtedly have been encountered very soon. The broad area over which the aneurysm was densely adherent to the pulmonary artery would have required an entirely different plan of

procedure. Resection of the ascending aortic arch and homograft replacement, with cardiac by-pass, would permit elimination of the aneurysm as well as direct suture repair of the perforation into the pulmonary artery.

Summary

(1) A case of rupture of a syphilitic aneurysm of the aorta into the left pulmonary artery is presented with autopsy findings.

(2) The syndrome associated with this vascular catastrophe is characteristic and led to a clinical diagnosis which was confirmed by cardiac catheterization and aortography.

(3) Surgical repair of this lesion was attempted and the problems encountered are discussed.

Acknowledgments

The authors wish to express their appreciation for the assistance of Dr. Doris Escher of the cardiac catheterization unit, Dr. Hilda Laufer of the Laboratory Division and Dr. Adrian Kantrowitz who performed the aortography.

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Spontaneous Rupture of the Right Coronary Artery*

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SPONTANEOUS rupture of the coronary arteries may result from a variety of causes. The etiology may be a congenital defect, atherosclerosis, infection, polyarteritis nodosa, rheumatic fever, trauma, or aneurysm. Shortly after rupture, death occurs as a result of either cardiac tamponade, arrhythmia, or acute irreversible congestive failure. In the case presented, none of the usual etiologic factors was demonstrated. The only contributing factors were hypoplasia of the walls of the coronary arteries and a history of mild hypertension.

CASE HISTORY

R. B., a 75-year-old colored woman, was admitted to the Nashville General Hospital at 5:40 in the afternoon in a state of profound shock. On the day of admission, she completed her housework without difficulty and was about to leave the house at 9:00 a.m. when she collapsed. Her physician found her pulseless, comatose, and without measurable blood pressure. After receiving 22.5 mg of ephedrine and 1.0 mg of coramine, the blood pressure was recorded as 70/0. The patient had been in excellent health with the exception of mild hypertension for a number of years.

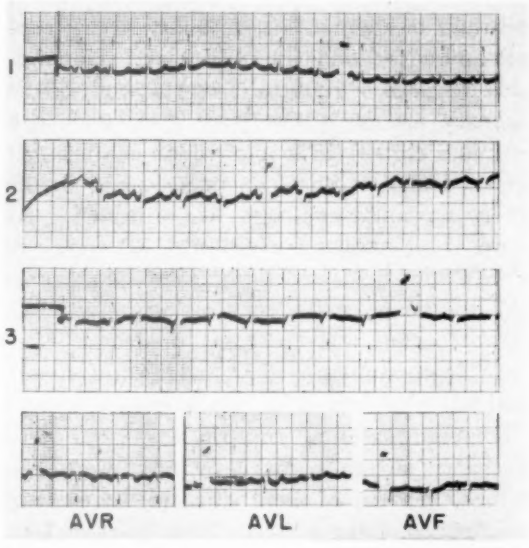

Fig. 1. Note the paroxysmal nodal rhythm throughout the electrocardiogram with slight changes in the P-Q segment in lead 2.

On arrival at the hospital the patient was stuporous, cold, and pulseless. The blood pressure was 40/0. Respirations were rapid and shallow. Abnormal physical findings were limited to the heart and lungs. There was dullness to percussion over the right lung base posteriorly with audible moist râles. The heart was enlarged to percussion 2 cm beyond the left midclavicular line. The rate was 120 per min and the sounds were of poor quality. There was a grade 1 blowing diastolic murmur audible along the left sternal margin. An electrocardiogram revealed periods of paroxysmal nodal tachycardia at a rate of 136 per minute with slight changes in the P-Q segment in lead II (Fig. 1). The patient remained in a state of shock despite the administration of stimulants, blood, and glucose solution, and she expired approximately five and one-half hours after admission.

POSTMORTEM EXAMINATION

Heart and Great Vessels: There was approximately 200 ml of bloody fluid in the pericardial cavity. The heart weighed 400 grams. The conus arteriosium contained an antemortem thrombus. There was an epicardial hematoma over the entire anterior wall of the right atrium. The chambers of the heart were dilated. There was a small interatrial septal defect measuring 0.5 x 0.25 cm. The endocardium was smooth and the valve cusps were normal. The right side of the heart was soft and left side was firm and moderately hypertrophied. The left sinus of Valsalva with its coronary ostium and artery were dilated and hypoplastic.

The right coronary ostium was patent. The right coronary artery in its course anteriorly along the base of the heart between the right atrium and ventricle

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had ruptured in a hypoplastic portion of the artery and produced a hematoma within the wall of the right atrium. The hematoma measured 2.5 × 1 cm and caused a bulbous projection into the lumen of the atrium. There was no evidence of aneurysm formation in the coronary vessels. The ascending aorta was unusually thin and dilated, measuring 6 cm in diameter. The pulmonary arteries were normal.

Microscopic Examination: Sections of the right coronary artery revealed very little atheromatous change. In an atrial branch of the right coronary artery adjacent to the hematoma, there was splitting of the media with hemorrhage into the area as illustrated in Figure 2. The actual point of rupture was not demonstrated microscopically. In Figure 3, taken near the site of rupture, there was hemorrhage and suggestive necrosis of cardiac muscle fibers, but no other evidence of myocardial infarction. Remarkably little atherosclerosis was present in the walls of these vessels.

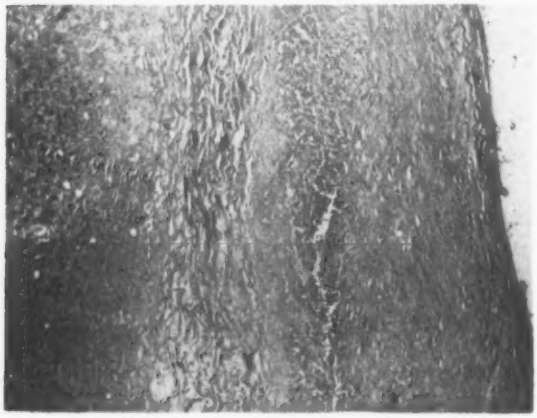

Fig. 2. Section of wall of atrial branch of right coronary artery showing splitting of media with hemorrhage (right foreground). A portion of the hematoma is shown on the left. (H & E Stain ×100 approx.)

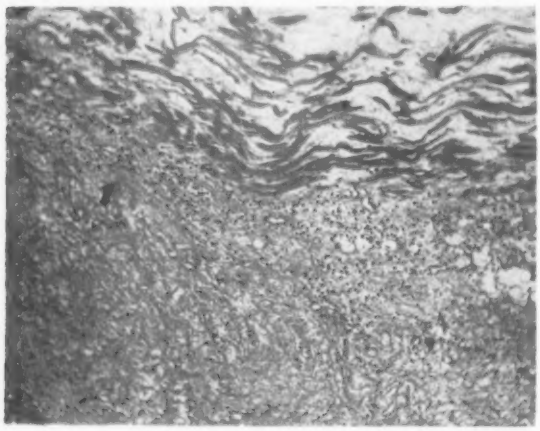

Fig. 3. Section of wall of right atrium showing a portion of the hematoma in the foreground. Note the edema and beginning necrosis of muscle fibers above. (H & E Stain ×160 approx.)

Microscopic sections from the arch and ascending aorta proved to be not over 0.4 mm in thickness. There was subintimal deposition of lipoid-laden monocytes. The thinned-out wall of the aorta showed a reduced amount of smooth muscle and elastic tissue fibers. The thickness of the aorta as seen in Figure 4A was approximately $^2/_3$ that of a similar section from a normal vessel, Figure 4B. Microscopic sections of the aorta did not show focal areas of necrosis as is usually seen in syphilitic aortitis or in extensive atherosclerosis. The smooth muscle and the elastic tissue fibers of the media were diminished in number, which was regarded as evidence of congenital hypoplasia.

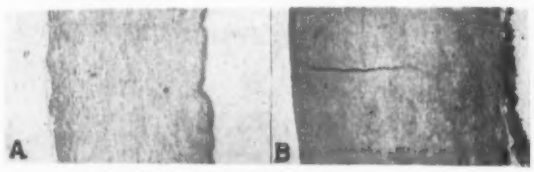

Fig. 4. A comparison of the thickness of the wall of the ascending aorta (A) with that of a normal aorta (B). Note the relatively slight atherosclerosis. (H & E Stain ×30)

Other Findings: Noncontributory.

Review of the Literature

A review of the literature failed to disclose any case similar to the one presented in this report. Olcott[1] in 1931 carefully reviewed the literature of spontaneous coronary artery rupture and added one case of his own. He tabulated 31 cases of rupture of one or both of the coronary arteries. Five were associated with infectious emboli, in four of which rupture had occurred at the site of aneurysms, and in the other, no aneurysm was demonstrated. At death these patients averaged 19.2 years of age. Two patients with syphilis showed aneurysmal dilatations in the right coronary vessel in which rupture was the cause of death. One was a Negro woman, aged 32, and the other a man aged 60.

Fourteen cases of rupture associated with atheroma of the coronary vessels were described. In ten of them, rupture occurred in the absence of aneurysms. Their age averaged 57 years. In four, rupture occurred at the site of aneurysms in atheromatous vessels. Among the three whose age was known, the average age was 71 years. Ten cases had ruptured

vessels without a known cause. One-half of them were associated with aneurysms. The average age at death in the two groups was 54 and 40 years, respectively. Olcott's patient exhibited a rupture of the circumflex branch of the left coronary artery, without an aneurysm, in a 60-year-old male. This patient died 15 hours after rupture from cardiac tamponade due to hemopericardium. The cause of the rupture was atherosclerosis and hypertension.

In addition to Olcott's review, Bamford[2] in 1931 reported two cases, one a 64-year-old white male with multiple aneurysms of the coronary arteries with rupture of one. Microscopic sections of the aorta were suggestive of luetic involvement. The second case was a 69-year-old white female who died suddenly and at postmortem a longitudinal tear of the left anterior artery was demonstrated. The cause was atheromatous. Vance and Graham[3] in 1931 reported a fatal case of hemopericardium following spontaneous rupture of the coronary artery in a patient with polyarteritis nodosa. Kowalczykowa[4] in 1934, Cortese[5] in 1935, and Dabrin[7] in 1944, each reported rupture of a coronary artery due to atherosclerosis. Giraud *et al.*[6] in 1936 reported spontaneous rupture of the coronary artery with resultant hemopericardium and death. The etiology was not stated. Kalbian[8] in 1945 reported the rupture of a coronary artery in the posterior wall of the left ventricle in a 62-year-old man. At the site of rupture there was a myocardial infarction. There was also considerable atherosclerosis of both main coronary vessels and the aorta. Including the present case, there are now 40 authenticated cases of spontaneous rupture of the coronary arteries described in published reports.

Discussion

After reviewing all cases in the literature, including our own, it is of interest to note that the actual site of rupture of the intima was rarely demonstrated. Examination of a microscopic section in several reported cases revealed a splitting of the media. Eskelund[9] and Lev *et al.*[10] state that aortic hypoplasia is not an uncommon congenital aortic anomaly and is usually associated with other congenital cardiovascular defects, often with a general hypoplasia of the arterial system.

In cases of rupture of the coronary arteries, the electrocardiogram may be of value in localizing the site of rupture. In our case, a paroxysmal nodal rhythm associated with slight changes of the P-Q segment in lead II was indicative of atrial pathology; findings which may also be found with acute atrial infarction.

The chief value of this case is to indicate the possibility of such occurrences in aged patients with a negative history of significant heart disease, and to illustrate an unusual explanation for acute cardiac death.

Summary

A case is reported of spontaneous rupture of the right coronary artery in a 75-year-old woman with hypertension and hypoplasia of the aorta and coronary vessels.

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Atrial Septal Defects in Elderly Patients

Report of Three Patients Aged 68, 72 and 78*

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ATRIAL septal defects are often not suspected in the aged. The clinician is frequently reluctant to diagnose congenital heart disease in the elderly patient. He may also be misled by history or symptoms of acquired heart disease which may alter the classic clinical manifestations of the underlying congenital defect. Nevertheless, it has been known for many years that functionally significant atrial septal defects are compatible with longevity.[1] They are the most common congenital lesions seen past middle life[2,3] and the percentages of patients living beyond age 50 vary from 25 to 50 per cent.[4–6] In 1864, Hüter[7] reported a patient with atrial septal defect who lived to the age of 65, and in 1880 Firket[8] recorded a woman who had eleven pregnancies and lived to be 74 years of age. Subsequent observers[2,5,6,9–16] have noted many such patients who lived well past middle age, some to 80 years and beyond. A recent report by Lyons and Kelly[2] re-emphasizes these facts.

The purpose of this presentation is to report three such patients, aged 68, 72 and 78, respectively, who were observed within a period of nine months. In the first two cases an intracardiac shunt was suspected clinically but no definite diagnosis as to the nature of the shunt was made. Because of recent experience with the first two, a diagnosis of atrial septal defect was made in the third. All were shown at autopsy to have large atrial septal defects of the ostium secundum type. None of these patients underwent cardiac catheterization.

CASE REPORTS

CASE 1. J. S. This 68-year-old white male was admitted to the Stamford Hospital for his terminal illness on May 28, 1956, with a diagnosis of arteriosclerotic heart disease and possible myocardial infarction. He had had numerous previous admissions for such complaints as attacks of fainting, palpitations, general weakness and occasional pain in the arms. The spells of syncope were usually evanescent and were never observed by a physician.

During several years of observation he had tolerated a number of major operations without incident and had had only one unrelated episode of frank congestive failure which responded well to digitalis. He was known to have a systolic murmur which was heard at the apex as well as in the second left interspace. Except during the episode of frank congestive failure his heart had not appeared enlarged on routine x-ray visualization, but "hilar masses" were described by radiologists on several occasions (Fig. 1). Electrocardiograms dating back to 1948 initially revealed complete typical right bundle branch block and thereafter "incomplete atypical right bundle branch block." At no time was

Fig. 1. Case 1. There is prominence of the intrapulmonary segments of the pulmonary arteries and some enlargement of the pulmonary conus. There is no significant change in size of the cardiac silhouette. (Film taken June 2, 1956.)

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there definite electrocardiographic evidence of myocardial infarction (Fig. 2).

During his terminal admission a systolic and a diastolic murmur were heard in the second left interspace and there was an accentuated second pulmonary sound. This was verified by stethogram. Routine chest films showed no variation over previous examinations. The above described "hilar masses" were considered to be due to enlargement of the first intrapulmonary segments of the pulmonary arteries. The left atrium was not enlarged, while the right appeared enlarged as did the left ventricle. Electrocardiograms during the terminal admission showed no essential change over previous records and there was no evolution of evidence of myocardial infarction. The patient's course in the hospital was uneventful. On June 11, the day of his death, he complained of severe chest discomfort and expired suddenly.

A postmortem examination showed the following: Moderately large atrial septal defect of the ostium secundum type (2.5 cm); recent thrombosis of the left coronary artery; marked sclerosis of the coronary arteries; old infarction (scarring) of the posterior part of the interventricular septum and scattered diffuse fibrosis throughout the myocardium. There was enlargement of the right auricle as well as of the right and left ventricle.

The heart weights were as follows: Total heart weight, 635 g. Left ventricle, 255 g. Right ventricle, 130 g. There was excessive amount of fat.

Case 2. F. L. This 78-year-old white male was admitted for his terminal illness to the St. Joseph's Hospital on December 14, 1956. He died less than 48 hours later. The reason for his admission was congestive heart failure with marked dyspnea and edema of the legs. He gave a history of having had rheumatic fever at age 24 and bouts of congestive failure for the past eight years. He had undergone major surgery (prostatectomy) five months prior to his death.

Examination of this somewhat cyanotic, dyspneic and orthopneic patient revealed the following essential findings: Blood pressure 150/90; pulse 108, grossly irregular due to atrial fibrillation. There was cervical vein distention and pulsation. The heart was markedly enlarged to the right as well as to the left. There was a grade 2 systolic and a diastolic murmur audible in the pulmonary area and the second pulmonary sound was accentuated. There was a systolic murmur at the apex which was transmitted to the axilla. One examiner thought he heard an opening snap. No friction rub was heard. There were moist crepitant rales at the bases of the lungs. The abdomen was moderately distended. The liver was four fingers below the costal margin. There was 3 plus ankle edema extending up the thighs and into the presacral area.

X-ray examination of the chest showed an enlarged heart with prominent pulmonary conus and markedly distended pulmonary arterial tree (Fig. 3). There was right ventricular enlargement and the right atrium seemed to be considerably distended. Review of x-ray

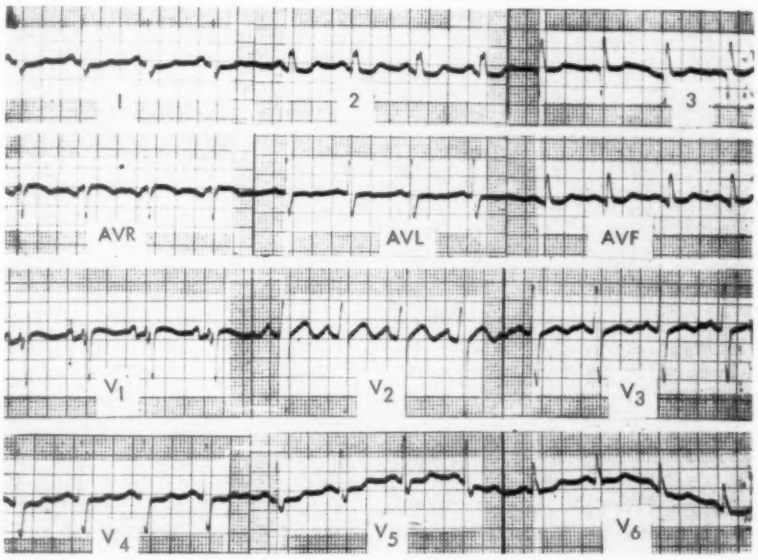


Fig. 2. Case 1. RSR′S′ pattern in V_1; QRS duration 0.10 sec; prominent P waves; normal electrical axis; "atypical incomplete right bundle branch block." Sinus rhythm. At postmortem examination, left as well as right ventricular hypertrophy, arteriosclerotic heart disease with healed myocardial infarction and recent coronary thrombosis without infarction were found in addition to the ostium secundum atrial septal defect.

Fig. 3. Case 2. Marked distention of the pulmonary arteries and of the pulmonary conus. There is considerable cardiac enlargement to the left, primarily due to increase in right ventricular size. (Film taken March 31, 1956.)

films taken on previous admissions showed essentially similar findings.

The electrocardiogram revealed right ventricular hypertrophy as characterized by "incomplete right bundle branch block" and atrial fibrillation (Fig. 4).

The patient improved with slow redigitalization and mercurials and had a satisfactory diuresis during the first night. He expired suddenly the following night.

Postmortem examination revealed the following: Heart weight 850 g. There were reddish-grey, granular, fibrinous adhesions between the pericardium and the epicardium. There were two large interauricular septal defects of the ostium secundum type, measuring 3 and 4 cm in diameter, respectively. The left atrium was only slightly distended; the right atrium was markedly enlarged. The left ventricle was not hypertrophied; the right ventricle was considerably hypertrophied and dilated. There was slight shortening of the chordae tendinae of the mitral valve which admitted three fingers with ease. The aortic valve was normal. The pulmonary valve ring was dilated and the major branches of the pulmonary arteries were markedly distended. There were scattered atheromatous deposits on the intimal surfaces of the pulmonary arteries. The tricuspid ring was considerably dilated and measured 15 cm in circumference.

Case 3. W. D. This patient who at the time of his death on March 2, 1957 was 72 years of age was first seen eight years before at the Stamford Hospital Cardiac Clinic for cardiac decompensation and right ventricular failure. He presented a history of rheumatic fever at 16 years of age and "asthma" since age 22. He had had nocturnal swelling of his ankles for 20 years prior to the time of his first visit. Physical examination at that time revealed a loud systolic murmur at the apex, transmitted to the axilla. On one occasion there was said to have been an apical systolic thrill; the second pulmonary sound was louder than the second aortic. His blood pressure was 110/68. The neck veins were distended, the liver was enlarged and there was moderate peripheral edema. A few weeks later a note by the same observer drew attention to the absence of a murmur at that time and the absence of the previously felt

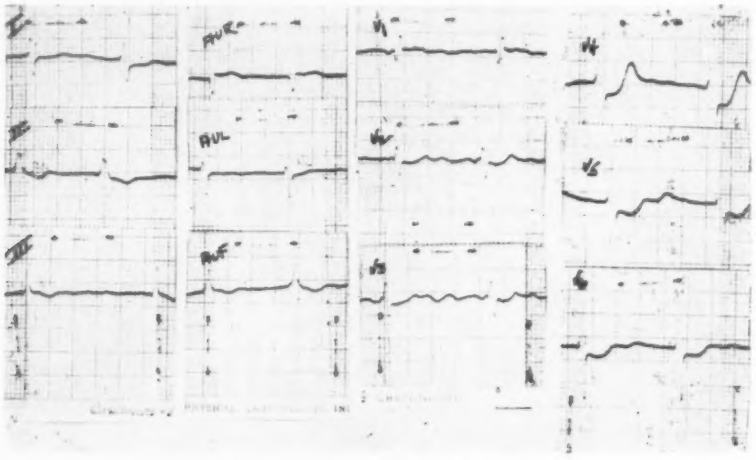
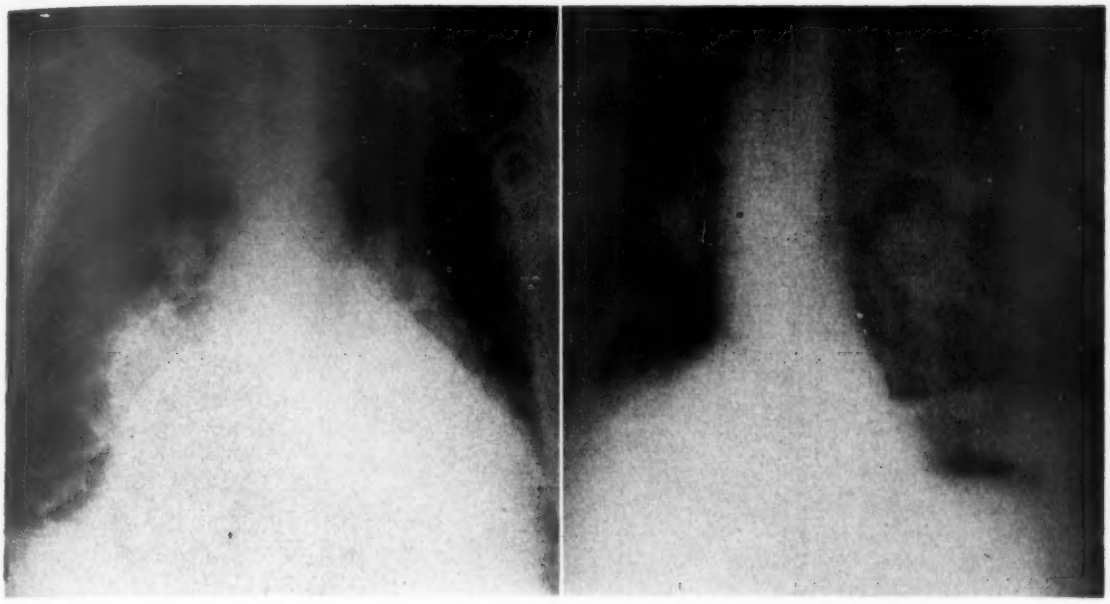


Fig. 4. Case 2. RSR′ pattern in V_1; QRS duration 0.09 sec. Evidence of marked right ventricular hypertrophy. Atrial fibrillation.



A B

Fig. 5A. Case 3. Tremendous enlargement of the intrapulmonary branches of the pulmonary arteries, prominence of the pulmonary conus. Globular enlargement of heart, due to marked increase in size of right ventricle and right atrium. (Film taken January 30, 1957.) (B) Case 3. Marked enlargement of pulmonary arterial tree simulating angiocardiogram. (Bucky film of chest and abdomen taken for possible intestinal obstruction, January 30, 1957.)

thrill. Fluoroscopic examination showed a generally enlarged heart, "bilateral hilar masses, hilar congestion and fibrosis." There was enlargement of the right ventricle. There was questionable enlargement of the left ventricle and the left atrium. Electrocardiograms taken over the eight-year period of observation consistently showed right ventricular hypertrophy as characterized by increasing "incomplete right bundle branch block." Many of these electrocardiograms also showed atrial fibrillation. The working diagnosis was rheumatic heart disease, mitral stenosis and insufficiency, arteriosclerotic heart disease (because of occasional attacks of angina), bronchial asthma, pulmonary fibrosis and chronic cor pulmonale. During the period of observation in the clinic the patient's physical, radiologic and electrocardiographic findings remained the same. With the above mentioned exception, an apical systolic murmur of grade 3 intensity, transmitted to the axilla and also heard at the left sternal border, was noted by all observers. At one time the diagnosis of congenital heart disease was suggested by a radiologist. Other radiologic reports, however, mentioned hilar lymph node enlargement as an explanation for the large "hilar masses."

The patient was treated in the usual manner with digitalis, mercurials and sodium restriction, with moderate improvement. The wheezing in the chest was relieved by Tedral®.

During the course of observation he had 13 hospital admissions for congestive failure which generally improved with bed rest, mercurials and phlebotomy. The electrocardiograms remained essentially the same except for the increasing incidence of multifocal ventricular premature contractions. Shortly before the patient's death his chest films were reviewed (Fig. 5A,B) and because of their similarity to those of case 1 and case 2, it was suggested that this patient probably had a large atrial septal defect. This opinion was based on the extreme enlargement of the intrapulmonary segments of the pulmonary arteries, prominent pulmonary conus, marked right ventricular and right atrial enlargement in the absence of significant left atrial enlargement, and the opinion was strengthened by the electrocardiographic findings of "incomplete right bundle branch block" (Fig. 6). A few weeks later the patient came to a sudden death at his home.

Postmortem examination showed the following: The heart was greatly enlarged. The interatrial septum showed several defects; the major one measured 4.2 cm by 2.5 cm in diameter and was of the ostium secundum type. In addition to this there were three fenestrations of the septum below and to the left of the major defect, measuring less than 1 cm in diameter and one single fenestration above measuring 1 cm in diameter. The right atrium and the right ventricle were markedly dilated and hypertrophied. The left atrium and left ventricle appeared to be about normal in size and configuration. The pulmonary artery was markedly dilated and the pulmonary valve when spread flat measured 6.5 cm in circumference; the aortic valve

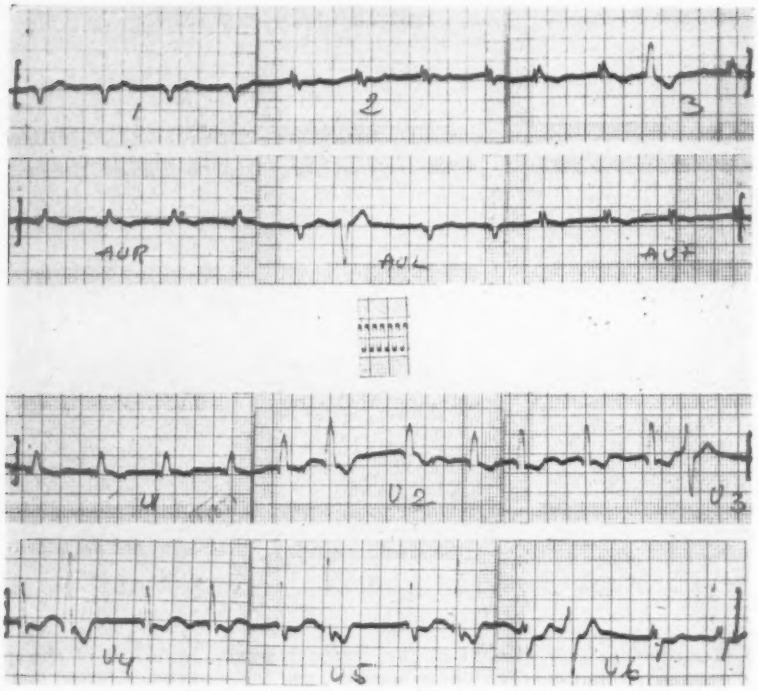


Fig. 6. Case 3. RSR′ pattern in V_1; QRS duration 0.11 sec. Marked right ventricular hypertrophy. Nodal rhythm, with 2:1 heart block. Multiple ventricular premature contractions. (Precordial leads recorded at half standardization.)

measured 3.5 cm in circumference. The mitral valve revealed a few small firm verrucous nodules on the free edge of the posterior leaflet and minimal shortening of the mitral chordae. There was dilatation of the tricuspid valve. The heart weights were as follows: Total weight, 634 g. Left ventricular myocardium, 153 g. Right ventricular myocardium, 257 g. Left atrial myocardium, 22 g. Right atrial myocardium, 51 g. Fat and valvular apparatus, 151 g.

Discussion

Three cases of atrial septal defects in the elderly are reported. In two, the diagnosis was confused by a history of rheumatic fever and the presence of atrial fibrillation; in the third, by arteriosclerotic heart disease. The effects of the long standing left to right shunt and marked increase in pulmonary flow, however, dominated the radiologic, electrocardiographic and some of the clinical findings. The diagnosis of atrial septal defect should seriously be entertained in elderly patients, even if there is evidence of acquired heart disease, when the following findings are present: Systolic and occasionally diastolic murmur in the second left interspace often accompanied by an accentuated second pulmonary sound; radiologic evidence of an extremely dilated, pulsating pulmonary arterial tree, and of combined right ventricular and right atrial enlargement, generally without significant increase in the left atrial size;[4,5,17,18] electrocardiographic evidence of marked right ventricular strain or hypertrophy of the outflow tract, frequently though erroneously called incomplete right bundle branch block.[19,20]

In addition to these findings there frequently is evidence of longstanding right ventricular failure.[5,11] Occasionally there will be a history of a thrill or bruit. The total absence of murmurs in these defects has been described by some authors.[21,22] Incidentally, these patients may withstand major surgical procedures rather well.[16]

A history of rheumatic fever should not detract from the suspected diagnosis since a large percentage of patients with atrial septal defect present such a history.[4] Roesler,[4] among others, has pointed out that atrial fibrillation is frequent in patients suffering from atrial septal defects, while it is absent in association with other congenital lesions. This is probably due to the

frequent coexistence of atrial septal defect with rheumatic heart disease. He reports that 28 out of 62 cases reviewed showed evidence of atrial fibrillation and 22 of these 28 cases, or 78 per cent, had rheumatic valvular deformities. Functionally significant mitral stenosis, however, is infrequent in atrial septal defects and true Lutembacher syndrome[9] is rather rare as was emphasized by Edwards[23] and others.[3,15]

With progressing age the incidence of other complicating acquired heart disease increases in these patients probably at the same rate as in the general population and may modify some of the above noted signs and symptoms.

Since functionally significant atrial septal defects are compatible with longevity, they should be included in the differential diagnosis in elderly patients when some of the listed classic findings are present, even though there are symptoms or history suggestive of acquired heart disease.

Summary

Three cases of atrial septal defect in the elderly are presented and diagnostic criteria are discussed.

Acknowledgments

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Historical Milestones

Excerpts from a Lecture by Carl Gerhardt on Haemorrhagic Infarction of the Lungs (1875)

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A SALIENT characteristic of the present medical scene in America is an intense interest, both clinical and experimental, in all forms of vascular disease. This interest is attributable to many causes, such as the increased frequency of vascular diseases and the frequently dramatic and alarming character of the symptoms. The latter traits are abundantly observable in cases of pulmonary embolism.

Carl Gerhardt's lecture on haemorrhagic infarction of the lungs represents nineteenth-century German medical instruction at its best. The excerpts which appear herewith have been selected both for their intrinsic and their historical interest, although, while conveying an adequate sense of the attractiveness and clarity of the original, they can hardly do justice to its thoroughness. The original text, titled Die hämorrhagische Infarkt, appeared in *Sammlung klinischer Vorträge*, Leipzig, 1875, no. 91 (Innere Medizin no. 31), pp. 721–738. The English translation, which is excerpted herewith, appeared in a volume entitled Clinical Lectures on Subjects Connected with Medicine, Surgery, and Obstetrics, by Various German Authors. . . Second Series. London, The New Sydenham Society, 1877, pp. 261–282.

Carl C. A. J. Gerhardt (1833–1902) was one of the most eminent nineteenth-century German clinicians and diagnosticians and occupied important academic positions at Jena, Würzburg, and Berlin. His principal writings deal with physical diagnosis, pediatrics, and laryngology.

GERHARDT ON HAEMORRHAGIC INFARCTION OF THE LUNGS

Gentlemen—You had the opportunity during last session of seeing a considerable number of cases of haemorrhagic infarction of the lung on the post-mortem table, and these cases were specially worthy of attention, because they had furnished at the bed-side well-marked symptoms of this affection. We observe these infarctions in cases of disease of the heart mostly, where their appearance usually introduces the last phases of a long illness, and often leads to one of the darkest scenes of human suffering. We may be tempted to look upon the infarction as a *modus moriendi* of heart cases, just as certain forms of pneumonia regularly develope in cases of slow suffocative death. . . . There are not a few anatomical results, and certain convincing clinical observations which point to cured or curing infarction in cases of heart disease. But if we leave out of consideration heart disease, and if we pass over pyaemia, we meet with the infarctions, somewhat more rarely indeed, yet frequently enough to recognise it as a comparatively mild disease, and one which under favourable circumstances is eminently curable. . . .

The Act of Embolism may occur almost or altogether without symptoms, where only very small and few coagula pass into a perfectly sound lung, or when there is already a strongly marked dyspnoea. Very large or massive emboli introduced simultaneously cause sudden death, or unconsciousness with convulsions ending in death. Between these extremes lie the symptoms which in very various degrees indicate the obstruction of a portion of the pulmonary vascular system, and generally precede the proper symptoms of infarction. The more extensive the closure of the pulmonary artery, the more certain is the *attack of unconsciousness*, which opens the scene. . . .

Shortly after such an attack, we find the patient very much altered, the agony of death in his features, which are sometimes pale, sometimes waxy white, or sallow, sometimes pale and leaden in hue, or with a marked increase of a previously existing cyanosis. A narrowing of the pulmonary artery suddenly arising makes the arteries empty and the veins overfilled. The skin of the extremities, often of the whole surface, is cold, and covered with a clammy sweat. The radial pulse may be absent, at any rate it is small, empty, and without tension. . . .

Soon after the beginning of the attack there developes a very violent *dyspnoea*. If the fainting is absent, then this is the first symptom, otherwise it immediately follows that symptom. Orthopnoea is commonly met with. The patient breathes with shoulders, with alae nasae, lower jaw, and the vertebral column is straightened and bent at intervals. But even these spasmodic efforts, the forcible movement of the chest and contraction of the abdomen, do not diminish the agony of suffocation. Every word, every movement increases the dyspnoea. The respirations are unusually close together, and reach a high number in the minute. Such dyspnoea as that may indicate of itself obstruction of the pulmonary arteries, if the temperature is low, if the percussion and auscultation reveal nothing, and if we can exclude affections of the haemoglobin itself.

While at the time such an attack gives the impression as compared with nervous dyspnoea of a very serious deep-seated affection of the respiration and circulation, so serious that it at once breaks down the strength of a powerful man, yet it is remarkable how completely the whole picture changes in one or at most two days. The portion of the pulmonary circulation which is still unobstructed dilates as much as possible, the pulse again developes to its proper fulness, the heat of the skin and the colour of the face return, the dyspnoea diminishes to a quite bearable extent, and obtrudes itself only on rapid movement. This is the case, at least in the first embolic attack, and where the thoracic organs are not in too unfavourable a condition. . . .

The bloody condition of the expectoration may be only transitory, and may be in the form of a mere trace, or it may last a long time when attack is very violent—thus in two of our cases it lasted twenty-seven days. In infarction all forms of haemoptisis which you can distinguish may occur, none is excluded. . . .

Bloody sputa may be yielded by one infarction for several weeks. They contain for more than a week unaltered blood-corpuscles. After two or three weeks there appear however in the expectoration granules and crystals of haematoidin, so that this form of bloody sputum is also met with in the course of the infarction. After a variable time, often about one and a half to two weeks, the bloody sputa, which have become scarcer, assume a brownish red, or dark red colour, similar to that of currant jelly. The expectoration of bloody sputa most frequently calls attention to the existence of the infarction; we learn often, for the first time, on putting direct questions, that a shivering or dyspnoic attack has preceded. At the same time this form of sputum does not prove the existence of an infarction. It is not found in every case and is not always a sign of this affection. . . .

All subpleural infarctions give rise to *pleurisy* just as pneumonia does. Only the occurrence of a fluid exudation is much more frequent than in pneumonia. . . .

I have never seen a purulent pleuritic exudation proceed from a simple infarction, but very many sero-fibrinous, of which the greater number ran their course almost or altogether without fever. . . .

Very similar forms of expectoration occur under the following circumstances:

(1) Frequent *ecchymoses of the bronchial mucous membrane*, such as often occur in heart disease with endocarditis of the left side. You will therefore only count the infarction as certain where you are able to determine the presence of dulness developing slowly during several days in one of the lower lobes.

(2) *Cancer of the lung* whose symptoms have been very well described by Koehler and Walshe, furnishes in the majority of cases, a few bloody sputa in the midst of many mucous ones. The former are intimately mixed, but very bloody, and somewhat of the colour of currant jelly. They resemble to a high degree

the sputa which are discharged after an infarction has existed long. . . .

(3) *Echinococcus* of the lungs must also be considered on account of the sputum intimately mixed with blood which it furnishes. . .

(4) The diagnosis of the infarction from *pneumonia* should never rest on an individual symptom, such as the appearance of the expectoration, the onset with an attack of dyspnoea or rigor, the presence or absence of high fever. Yet you may definitely hold the infarction as determined, if there obviously exists embolic material and an embolic attack, and when the diagnosis is confirmed by absence of fever, dulness in the lower lobe lasting for some weeks, and haemoptisis. In cases where the subjective distress is very slight and haemoptisis and a limited dulness in a lower lobe can be determined, we may very readily infer the existence of small infarctions. . . .

The *prevention* of diseases is doubtless a higher object than their cure. This applies also to the infarction. We possess indeed no means whereby to prevent the coagulability of the blood in the body, or to shut off thrombosed vessels from the circulation. This would be, if practicable, the most thorough means of prevention of the infarction. . . .

Much more dangerous for those who possess thrombi are rapid and frequent muscular exertions, or even unaccustomed movements. You should make convalescents with thrombosis in the calf lie undisturbed in bed till oedema and collateral dilatation have disappeared. An extremity with such thrombosis you should rather render immobile by mechanical contrivances, such as wadding with a starch bandage over it. . . .

We have most frequently to treat that violent state of dyspnoea which lasts a number of hours after the embolic closure of a medium-sized vessel. The subcutaneous injection of morphia is shown to be a wonderfully active remedy and one which gives immediate relief, it deserves as yet the preference before all others. . . .

To those who consider that an energetic therapeutics is the only worthy task of the physician, the treatment of the infarction will afford little pleasure. . . .

Myocardial Infarct vs. Myocardial Ischemia in Paroxysmal Tachycardia

The Diagnostic Value of Carotid Sinus Pressure

A 59-year-old white male came to the Hospital complaining of dizziness and precordial pain of four hours' duration. He gave a history of hypertension for several years. He had been hospitalized 21 years before for a nondefined "heart attack"; his hospitalization lasted three weeks. In the past five years, he suffered from repeated episodes of dizziness accompanied by precordial distress.

Physical Findings: Physical examination revealed a well-developed man with a flushed face, a regular pulse of 130, and a blood pressure of 200/120. The heart was enlarged to right and left on percussion, and a grade 2 systolic murmur was heard over the entire precordium. The heart tones were of good quality and there was a diastolic gallop sound at the apex. The lungs were clear, the liver was barely palpable. There was no orthopnea, dyspnea, or cough. Four hours later, the pulse was still 130 but the blood pressure had dropped to 110/80.

ECG Findings: Suspecting a myocardial infarct, the resident recorded an electrocardiogram. This showed left axis deviation, no evidence of ventricular hypertrophy, and a pathological rhythm which was interpreted as a *supraventricular tachycardia* (positive TP wave in diastole). There were no Q waves or inverted T waves but the S-T segment was depressed in V_2-V_6 and all limb leads.

Clinical Diagnosis: The differential diagnosis took into consideration two possibilities:

(a) An acute myocardial infarct followed by supraventricular tachycardia.

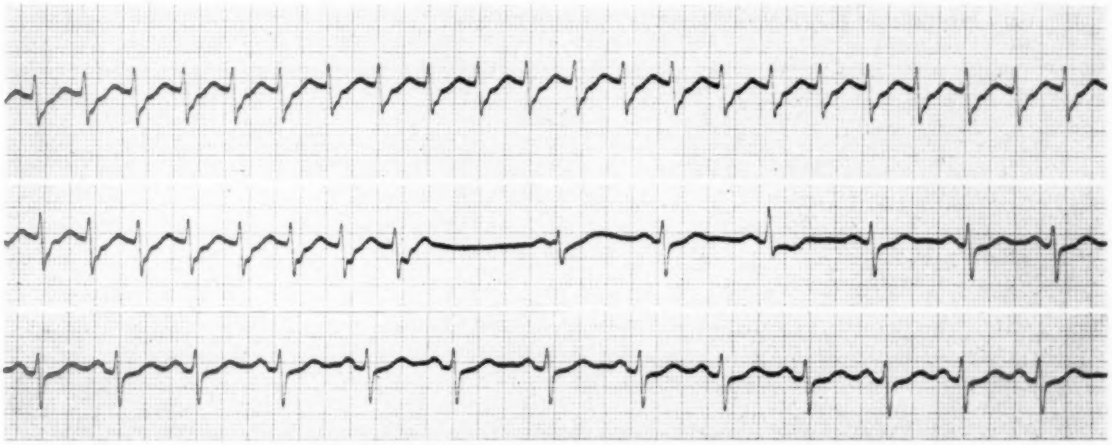

Fig. 1. Electrocardiogram in lead 2. Effect of massage of right carotid sinus. Upper strip—Before (supraventricular tachycardia). Center strip—During massage of carotid sinus (return of sinus rhythm). Lower strip—one minute later (sinus rhythm).

(b) A supraventricular tachycardia with secondary myocardial ischemia.

Effect of Carotid Sinus Pressure: Interruption of the attack by reflex action was discussed. Some feared that strong vagal stimulation might be detrimental if there was an infarct. The latter was not excluded because the electrocardiogram may not be diagnostic in the first few hours; moreover, the tachycardia might mask a typical pattern.

In spite of these objections, reflex stimulation was undertaken. Compression of the eyeballs did not slow down the cardiac rate. *Massage of the right carotid sinus*, on the contrary, was followed by sudden slowing of the beat and by resumption of sinus rhythm (Fig. 1). Following this, a 12-lead electrocardiogram was recorded. A slight depression of S-T was present, and there was inversion of the T waves in all leads, most marked in V_4-V_6. This was interpreted as the result of diffuse ischemia (*post-tachycardia syndrome*) in a patient with hypertensive heart disease.

Reflex slowing of the heart rate and resumption of the sinus rhythm were considered to have been useful by removing a severe strain on the myocardium and proving the nonexistence of an infarct.

The patient returned home after 24 hours, after having been placed on a maintenance dose of quinidine.

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Readers are invited to submit reports of interesting cases and illustrative tracings for this department. These should not exceed 1,000 words in length. Although not necessarily original, all material submitted should have teaching value.

Coming in the July Issue . . .

Symposium on Mitral Regurgitation (Part I) . . . Cardiac Drug Responses and Potassium Shifts . . . The Anatomy of Chest Pain . . . Acute Myocardial Infarction in a City Hospital. II. Experience with Anticoagulants . . .

Progress Notes in Cardiology

Editd by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

Ligation of the Internal Mammary Arteries as a Possible Means of Increasing Myocardial Blood Flow

THE possibility of increasing myocardial blood flow in patients suffering from coronary insufficiency, by bilateral ligation of the internal mammary arteries at the level of the second intercostal spaces was originally proposed by Fieschi in 1939 and again by Battezzati, Tagliaferro and De Marchi in 1955. The rationale of this procedure is an attempt to divert some of the arterial blood which flows down the internal mammary arterial system into the pericardiophrenic arterial system to the pericardium. From here the blood flows through variable channels under the epicardium to the peripheral radicals of the coronary vascular bed. That such collateral channels exist to a variable degree has been known since Langer's early report in 1880.

In Battezzati's initial report, 11 patients were treated by this surgical technic, with partial or complete relief of angina pectoris. Since then, numerous studies have been made in an attempt to determine the value of internal mammary artery ligation. Results have been variable. A recent report by Kitchell, Glover, and Kyle appeared in this JOURNAL (1: 46, 1958). Another series of observations has just been reported by Drs. Charles R. Blair, Robert F. Roth, and Harold Zintel (St. Luke's Hospital, New York). They first made experimental studies on dogs to determine the effect, if any, of internal mammary artery ligation on coronary blood flow. Dogs placed on an oxygenator-pump apparatus had their coronary flow measured before clamping the aorta, after clamping the aorta (distal to coronary artery takeoff), and with both aorta and internal mammary arteries clamped in the 3rd interspace. Coronary flow was measured by collecting all the blood returning to the right side of the heart. A constant perfusion pressure of 100–110 mm Hg was maintained. Baseline flows, before aorta was clamped, averaged 100 ml/min volume. In acute experiments with the aorta clamped, this flow dropped to about 1 ml/min volume, regardless of whether or not the internal mammaries were clamped. In long term experiments in dogs that had their internal mammary arteries tied off six months previously, coronary flows, with aorta clamped, averaged 9.6 ml/min volume. If the internal mammary arteries were then temporarily occluded at their origins, this flow would drop to less than 1.0 ml. Release of mammary occlusion returned the flow to its previous level, i.e., 9–10 ml.

Six humans in Blair's study have had bilateral internal mammary artery ligation in the 2nd interspace for a sufficient period of time (over six months) to evaluate the results. Two patients claim complete freedom of pain and have returned to their former work. One claims moderate improvement with less pain and fewer nitroglycerin tablets. Two are unchanged. One died seven months post-ligation of a myocardial infarction. However, this last patient, a man 73 years of age, said his pain was less following ligation. It is of interest to note that those patients who are unchanged actually claimed immediate postoperative improvement

which regressed in two to three months, while those who got the best results took two to three weeks before the improvement became apparent.

In another recent paper, Dr. Ralph Adams (*New England J. Med.* 258: 113, 1958) casts doubt on the ability of this procedure to increase coronary artery blood flow despite the fact that patients may experience symptomatic improvement. He points out that the patient's will to get better, his belief in the physician's word, and his confidence in the operation are more important factors than we generally accept.

Palmar Pulsation—A Physical Sign of Patent Ductus Arteriosus in Infants

THE recognition of patent ductus arteriosus in infants is difficult. If the infant fails to thrive or shows signs of congestive heart failure, the problem of diagnosis becomes very important, because of the possibility of surgical treatment and cure. Often the murmur is not typical, either in character or in site of maximal intensity, and reliance must be placed on x-ray signs, such as a prominent pulmonary artery and hypervascularity of the lung fields, or on peripheral arterial signs, such as large amplitude pulses of a collapsing quality, and a wide pulse pressure. However, it is often difficult to take accurate blood pressure readings by the cuff method in a small child.

Dr. D. Stuckey (*M. J. Australia* 2: 681, 1957) has described the physical sign of palmar pulsation in such cases, as an aid to making the diagnosis of patent ductus arteriosus. This consists of a forceful pulsation of the superficial palmar arch, as it crosses the heads of metacarpal bones. This sign is uncommon in normal infants from birth to two years of age. It becomes increasingly common in older age groups.

Palmar pulsation is related to the pulse pressure, and is almost always present if the pulse pressure exceeds 50 mm Hg. (In cases of patent ductus arteriosus, the pulse pressure is usually greater than 50 mm Hg.) However, any condition which produces peripheral vasodilatation and an increased cardiac output is accompanied by a large pulse pressure. Common conditions of this type affecting infants are fever, anemia and high environmental temperatures (higher than 80° F). If these conditions are absent in an infant under two years of age, and palmar pulsation is present, a patent ductus can be suspected. Conversely, absence of palmar pulsation in a child under two years of age, suggests that a patent ductus arteriosus is *not* present.

Cardiac Resuscitation

Edited by PALUEL J. FLAGG, M.D.*

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Acute Respirocardiac Failure

A New Concept for the Cardiologist Which Demands Timing and Speed

ANNOUNCEMENT OF a NEW SECTION AND COMMITTEE

AT THE 25th annual meeting of the Board of Directors of the National Resuscitation Society, Inc., February 17, 1958, it was suggested that contact be established with The American College of Cardiology for the purpose of exchanging views concerning the prevention and treatment of respirocardiac failure. It was furthermore proposed that the Society provide the JOURNAL of the College with material for publication and that active cooperation be extended to any Committee which the College may see fit to appoint. These proposals were submitted to Dr. George R. Meneely, President of the College, on March 13, 1958. With characteristic courtesy and promptness Dr. Meneely replied on March 20: "I entirely agree with you that cooperation with the American College of Cardiology would be immensely useful. I have talked on the telephone with Dr. Claude Beck who stated that he was willing to accept Chairmanship of a Committee of the American College of Cardiology for the purpose of setting up an active cooperation with your Society. I also think that it is a splendid idea that information on this subject should be published in the JOURNAL." On March 27, in a conference with Dr. Simon Dack, Editor of the JOURNAL, Dr. Paluel J. Flagg, speaking for the National Resuscitation Society, Inc., agreed to assist through the coming year in providing material for a new Section of the JOURNAL, "Cardiac Resuscitation".

Since new movements as well as individuals and groups may be judged by their philosophy, their tactics and their goals, an attempt will be made in this first release to state frankly just what we believe will make this Section tick, how it hopes to be useful, and what it considers to be its objectives.

PHILOSOPHY

The importance of cardiac failure is rapidly emerging in the medical and lay press as a major issue. The dramatic impact of open chest cardiac message as an emergency measure in cardiac arrest and fibrillation, is developing repercussions in the operating room, in the emergency ward and in the ambulance service. The lay press eagerly reports details of the latest attempt to bring a victim, clinically dead, back to life, by the simple procedure of opening the chest and squeezing the heart.

As physicians, curious about the causes of such catastrophes and more or less familiar with the pathologic etiology precipitating these accidents, the conviction is growing that there is something wrong in this new rash of cardiac tragedies, that something is missing, something conspicuous by its absence. This missing link, which looms larger and larger as we become

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aware of it, is the respiratory factor. Since most cardiac arrests occur as the result of hypoxia of the myocardium (excluding sudden fibrillation due to coronary occlusion), which sensitizes it to arrest or fibrillation by numberless triggering causes it seems of first importance that prolonged hypoxia from any cause be prevented and when it does occur that it receive first attention. Of what use is it to re-establish a circulation bereft of oxygen? Under such circumstances what hope is there of restoring normal rhythm and blood pressure?

Some time ago an ambulance surgeon was called to the side of a patient who had hanged himself. He had been cut down and was found to be pulseless. The first aid squad was doing artificial respiration. The patient's chest was opened. There was no bleeding. After ten minutes of massage, a spontaneous rhythm of about 100 was established. The patient was placed in an ambulance and taken to the hospital. An attempt was then made to laryngoscope and intubate him. This was found to be difficult and ten more minutes elapsed before the lungs were expanded. Fibrillation of the heart followed rhythmical contractions and the heart then went into standstill. Without doubt the surgeon who attended the patient had in all good faith followed the present drift of misdirected enthusiasm and had set a perfect example of doing the last thing first.

In hanging, swelling and distortion of the soft parts of the airway take place promptly (see illustration 238, *Art of Resuscitation*, Flagg, P. J., Reinhold Publishing Co.). Landmarks of the airway are distorted, exposure and intubation are difficult. If immediate cricothyroidotomy or tracheotomy had been done, with insufflation of air or oxygen into the trachea, alveolar oxygen might have found its way back to the myocardium and massage might have been successful. In such an emergency to await the arrival of an anesthetist is not only ridiculous but a tragically fatal error. Any man who can learn to look into an ear, a nose or a bladder can look into the larynx of a patient in the state of flaccid hypoxia accompanying cardiac arrest.

Stated briefly, therefore, the basic philosophy of our approach to the problem of acute respiro-cardiac arrest is *to shift the emphasis from cardiac to respiratory resuscitation.* If this philosophy is pursued the appalling need for opening the chest and massaging the heart is sure to be reduced. However, though the incidence of cardiac arrest declines, familiarity with the technic of open chest cardiac massage *must* become common knowledge, for hypoxia which has not been anticipated or controlled will too frequently take place and we will find the patient's heart and life in our hands.

Tactics

The means to be adopted for treating and for preventing acute respirocardiac failure are both immediate and long range.

The immediate approach consists of alerting the physician and all those responsible for the care of the unconscious patient to the nature of the problem and the simple technical means of dealing with it. Intensive courses, didactic, audio-visual and instrumental, in which dogs, anesthesized patients and cadavers are made available within a 24-hour period, along the lines followed in the course offered by the National Resuscitation Society, Inc. during the past ten years, should be multiplied over the country. It is our intention to present the highlights of this course in forthcoming issues of the Journal.

The long range approach has to do with the education of the medical student, the intern and the resident. It is essential that these men be indoctrinated, that is, alerted to a "doctrine," presently recognized by numerous groups but which has lacked formal sponsorship such as that of The American College of Cardiology, to which reference may be made as occasion offers. What is this doctrine? It consists of the demonstrable facts evident in progressive hypoxia. These facts or stages of progressive hypoxia, depression, spasticity and flaccidity, have been recognized by obstetricians during the last twenty years. They parallel the progressive stages of general-ether-anesthesia. They are characteristic of the progressive effects of obstructive croup in pediatrics. They are recognized by psychiatrists in shock therapy. While denial of these effects is not encountered, a positive enthusiastic support and promotion of this doctrine is essential because the stages of

progressive hypoxia represent the progressive physiologic pathology taking place at a given instant and this pathology in turn clearly indicates the exact treatments required. The doctrine referred to above, which has always been found acceptable on demonstration, needs the widest possible publicity and support, for it is the language of the diagnosis and the treatment required. The problem of placing this doctrine into the medical school curriculum has been discussed with the Association of American Medical Colleges. It is agreed that a direct, effective method would be to utilize a professional color sound film. There is an urgent need for funds for this purpose. Immediate production of such a film awaits the collection of funds. Material on which the script of the proposed film is based will appear in a later issue of the JOURNAL.

Finally, resuscitation apparatus and gadgets for resuscitation are to be regarded, as a scalpel or a hemostat is regarded, as a tool to bring about a desired effect. All resuscitation apparatus regardless of incidental variables fit into three patterns of specific usefulness, i.e., for inhalation, for transpharyngeal insufflation, and for endotracheal insufflation. The fluid pattern of hypoxia cannot be subordinated to any one apparatus or method. Simplicity is the keynote of usefulness. During World War II, a government production plant displayed a four-letter sign which attracted a good deal of attention. The sign read *KISS*. Below in small letters appeared the meaning—*Keep It Severely Simple.*

GOAL

The specific purpose of this new Section on Respirocardiac Failure is to help reduce the incidence of respiratory and subsequent cardiac failure. The combined death rate from these hazards is enormous. As Claude Beck has pointed out, the term *resuscitation* fails to convey the magnitude of or the nature of the problem. The movement which has now begun and in which we are all pioneers is in reality an anti-death movement. Hypoxia over the world may be compared to a great river, fed each year by one million deaths. This deep and somber stream finds its source in a mighty cascade of half a million babies who die each year from asphyxia at birth. On its course to eternity the river is swollen by tributaries, the drowned, those who die from poison gases, the electrocuted, the suffocated, anesthetic deaths, foreign body obstruction, deaths from drugs or one of the many other causes of asphyxiation.

The death rate from asphyxia in the United States is conservatively estimated as 50,000 a year. The population of the world is about 17 times that of the U. S. With existing primitive methods of prevention in many parts of the world, a death rate of 1,000,000 is realistic. Hypoxia cuts across the entire field of the practice of medicine. It is as universal as hemorrhage. Indeed hemorrhage is anemic hypoxia. Given the name of a specialty one may point out the hypoxia hazard common to it.

The next issue of the JOURNAL will discuss the difference between asphyxial death and asphyxia which occurs as a symptom. It will stress the need for an "asphyxia consciousness" in intramural accidents and the particular difficulties faced in extramural asphyxia accidents.

Questions addressed to this Section will be answered as promptly as possible.

Workmen's Compensation for the Cardiac

Strain, Trauma and Cardiac Disability

Proposed Views and Aims of the Committee

LOUIS H. SIGLER, M.D., F.A.C.C., *Chairman*

Brooklyn, N. Y.

IN TWO previous communications[1,2] an attempt was made to help solve the controversial compensation problem of causal relationship between strain and cardiac disability. In the discussion of the underlying pathology of an acute coronary insult it was pointed out that the clinical manifestations are not caused by the coronary disease per se but by the resulting myocardial changes due to interference with the coronary blood supply. The myocardial changes may be in the form of ischemia with or without ischemic necrosis, or in the form of gross infarction. The interference with the coronary blood supply may be due to narrowing or complete occlusion of a coronary branch by an expansion of an atheromatous plaque and/or by thrombosis. In some cases it may be due merely to physiologic disturbances caused by coronary angiospasm or by a variety of constitutional and reflex factors such as shock, tachycardia with or without severe arrhythmia, severe hemorrhage, and severe heart failure. As a reflex phenomenon it is also often observed after marked excitement in individuals with severe coronary atherosclerosis. Reflex disturbances from disease of abdominal organs, particularly of the gall bladder, may in some cases be the cause and at times perhaps linked with digestive disturbances. Strain is known to precipitate the condition in the presence of coronary atherosclerosis. In its milder form this can be easily demonstrated by work tolerance tests. In many such cases, if death occurs suddenly no complete occlusion is found at autopsy but merely chronic atherosclerosis with more or less narrowing of the lumen. If acute coronary insufficiency is severe and prolonged and the patient survives, myocardial necrosis or even massive infarction may develop. Autopsy during this phase may show the myocardial pathology with no complete coronary occlusion to account for it.

CRITERIA IN DETERMINING CAUSAL RELATION

The various pathologic conditions may be set up by physical and emotional strain, but because they frequently appear to occur also spontaneously, an attempt was made to establish certain criteria to be used in determining causal relationship between strain and a cardiac insult. The criteria were based on actual case presentations. It was felt that the strain must be unusual and of a type to which the claimant was not accustomed. In some cases, however, usual strain may result in injury provided it is severe enough and is experienced during a so-called vulnerable phase of coronary disease. The symptoms of cardiac injury must develop soon after the strain and continue. An attack of acute myocardial injury developing some time after an alleged strain cannot be attributed to that strain unless some symptoms developed soon after the strain and continued with greater or lesser severity until the acute cardiac manifestations occurred. Recurrence of a cardiac insult a long time after recovery from a cardiac in-

jury induced by strain cannot be attributed to the original strain. Work done under great emotional excitement and hurry may precipitate an attack in an individual with severe underlying coronary disease.

Sudden death after severe exertion is to be attributed to such exertion even if the postmortem findings do not reveal an acute occlusion of a coronary vessel, provided there is extensive coronary atherosclerosis. It could have been due to ventricular fibrillation or cardiac arrest caused by acute ischemia induced by the work. Death occurring years after an alleged cardiac injury may be traceable to such injury or to some other causes. A careful history and autopsy examination will be necessary to establish relationship in such cases.

It was also brought out that a greater or lesser degree of functional recovery of the heart after injury occurs in most cases, and the claimant may in many cases be able to work for a livelihood for many years. In some cases, however, partial or total disability may follow the injury for the rest of the claimant's life. The causes may vary in different cases and may consist of recurring or continuous arrhythmias; recurring ischemia and infarction; embolization from mural thrombi in the heart or from venous thrombosis caused by inactivity; angina pectoris; congestive heart failure; emotional disturbances due to fear of death; fear to return to work because of possible aggravation of the condition; and fear on the part of the family that work may shorten the claimant's life. In some cases the claimant finds it more advantageous to stay away from work if disability payments by the insurance company are adequate to take care of his needs, and he therefore feigns illness.

It was felt that in evaluating any claim for disability, the reliability of the claimant's history is most important. Claims for disability filed long after an alleged strain call for particularly careful investigation as to the reliability of the history. It must be determined if a given strenuous type of work has actually been performed; if the work claimed to have been done is not exaggerated; and, if some intervening event occurred, not the work, which precipitated the attack.

The response to these two papers revealed considerable interest on the part of the medical and legal professions and others concerned with the problem of workmen's compensation. Numerous letters were received from different parts of the country praising the approach to the subject. Many requested information on specific cases they had on hand. The response illustrates the desire of the medical and legal professions to get some concrete information on this important subject. It was particularly gratifying to get a request from the American Heart Association for a number of reprints to be distributed to the members of its Committee on Effect of Strain and Trauma on the Heart and Great Vessels. I believe that the committee will help decide if the views expressed in the two publications are justifiable and offer help in solving this vexing problem.

Another important response to these publications was the loss on my part of the patronage of some insurance companies who occasionally referred cases to me for consultation, opinion, and testimony. There were also rumors reaching my ears to the effect that some attorneys representing certain insurance companies were looking for someone to write a paper refuting my views. It was interesting to find that certain attorneys representing claimants likewise stopped sending me occasional cases because they felt I was antagonistic to their cause. I welcomed this event, for I consider complete impartiality in these cases the essence of ethical conduct. I always believed that regardless of how honest or ethical a physician may be, he may be tempted to color his views by some ulterior motives. In view of the fact that the processes involved in cardiac injury due to strain and trauma are mainly physiologic and cannot always be studied directly but only by inference from resulting clinical and anatomic findings, our opinions must necessarily be based to a great extent on theoretic consideration. Belief is thus the important element upon which opinions are based. Inasmuch as belief has many psychologic elements in its makeup, one of which is a subconscious and at times even a conscious desire for some remunerative gain, it necessarily may be influenced by this factor.

Evils and Defects of Compensation Practice

The reaction to the two papers illustrates the partiality practiced in these cases. The physician is evidently expected to favor the representative who pays the bill. Inasmuch as the law in many states does not allow the physician to charge a claimant of workmen's compensation for services or for testimony but is compelled to resort to the good graces of the referee and to a minimum schedule of allowed fees by the Labor Department, the claimant frequently has no opportunity to get proper scientific medical care or expert testimony. No first class internist or cardiologist cares to engage in compensation practice. On the other hand, the insurance companies who are willing and able to pay high fees without legal restrictions often attract reputable men for their defense. The possibility of maladministration of justice is thus great.

Another evil connected with compensation practice is that a physician is not allowed to charge a fee to a patient who claims that his illness is due to an alleged accident or strain, regardless of whether or not the claimant gives an honest history. He often has to treat the claimant for a prolonged period of time and waste valuable time filling out repeated reports until such time as the case finally comes for a hearing. If the referee rules in favor of the claimant, the insurance company has the right to appeal which again delays the decision for a considerable period of time. It is not unusual in cardiac claims for a case to drag on for one or two years until a final decision is reached. If the claimant is finally successful the physician often has his bill refused, contested, reduced, or questioned. Arbitration may be the ultimate recourse and the schedule of "legal" fees is the bible by which arbitration is determined. If on the other hand, the claimant loses the case, the physician has no other resort than to try to collect his fees from the claimant. In many such cases it means the end of the physician's fees. Court proceedings are often useless because of financial irresponsibility of the claimant in many cases. Such conditions must necessarily be causes of maladministration of justice, and in many cases are detrimental to the insurance company. There is perhaps no doctor who is willing to lose his hard earned fees by being in favor of the insurance company. Partiality is therefore probably frequently practiced in his testimony of causal relationships.

Another angle connected with the medical practice in compensation cases is to make the doctor return the fee he received from a patient for treatment if the claim is declared compensable. This applies even to a physician who was not engaged to treat the patient as a compensation case. It applies particularly to a consultant who might have seen the case once or twice and was paid by the patient. When the patient submits his paid bill to the insurance company, after compensability has been established, it is usual for the insurance company to tell the physician to return the fee to the claimant and then submit his bill to the company at a reduced compensation rate. One reason for this procedure is to reduce the physician's fee, even though it was fully earned and willingly paid by the patient who in many cases can well afford to pay the usual fee. Another reason appears to be the attempt on the part of the insurance company to discourage capable physicians from engaging in the compensation practice.

These are only a few of the defects in compensation practice. They illustrate the importance of further thorough study of the various angles in this practice to devise ways and means of their correction. As it is practiced today, both the claimant and the defendant often suffer from these defects. The claimant, as stated before, does not always get the proper medical care and testimony. The defendant often has to fight dishonest claims and attempt to overcome unsubstantiated medical testimony. In some cases, the duration of disability is longer than the claimant is entitled to. The result of this situation is unwillingness on the part of the employer to engage a worker in the arteriosclerotic age for fear that possible disability claims may result from work. This is particularly true if the worker is known to have some cardiac defect or a higher than average blood pressure.

The College Committee on Compensation

Realizing the importance of further study of the compensation problem of cardiac disability, Dr. Simon Dack in 1956, while president of the

American College of Cardiology, suggested that we form a committee for such study. In 1957, the incoming president of the College, Dr. George R. Meneely, continued the work of the committee and has also established a Committee on the Problems of Employment of the Cardiac Patient, under the able leadership of Dr. John R. Williams. Both these committees will work in cooperation in attempting to solve some of the problems of work and heart.

We realize that the problems are highly complex and there are no easy solutions to them. However, attempts must be made to arrive at some practical and universally accepted conclusions as to methods of determining causal relationship, and the elimination as much as possible of the present abuses in this field. If the views of causal relationship under the various conditions as set forth in the two previous communications and outlined above are acceptable they should help clear the ground for some solution to the problems. If not acceptable, other views must be openly expressed and adequately substantiated by fact.

255 Eastern Parkway

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1. Sigler, L. H.: Cardiac disability and death caused by strain: Problem in workmen's compensation. *J.A.M.A.* 154: 294, 1954.
2. Sigler, L. H.: The evaluation of claims for workmen's compensation in cardiac disability and death. *Ind. Med. & Surg.* 25: 10, 1956.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Anticoagulants in Strokes

Query: Do you use anticoagulants in cerebrovascular accidents?

Answer: Selectively, when we are dealing with an individual of not too high blood pressure with a tendency toward plethora and where the symptoms of the accident are intermittent; in short, when the individual has evidence of so-called "intermittent strokes," dizziness with minimal residues. We do not use them when there is a massive lesion fully established, where there is moderately elevated blood pressure, or where the blood count is severely reduced.

Cerebral Hemorrhage Due to Anticoagulants

Query: How often have you seen death from cerebral hemorrhage following use of anticoagulants for cardiac or cerebral disease?

Answer: We do not have the occasion to see many patients with cerebrovascular accidents who have been on anticoagulants. I have seen several with intracranial bleeding, usually subarachnoid, in the course of anticoagulant therapy, when the cessation of the therapy brought about a clearing up of the symptoms. In one instance, the patient came in with mental symptoms which were due to subarachnoid oozing, associated with the use of anticoagulants for cardiac disease. The syndrome cleared up with the discontinuation of the dicumarol. I have seen a number of deaths in patients with cerebrovascular diseases where anticoagulants were used. In some, the criteria of not using these in the presence of severe hypertension was disregarded; however, since cerebrovascular lesions have a tendency to recur it is hard to tell whether the patient might not have died anyway. The number is too small to form a final judgment.

Anticoagulants in Cerebral Thrombosis

Query: If you suspect cerebral thrombosis, how long should anticoagulants be continued?

Answer: This is too general a question. Thrombosis of what? If it is a fully established thrombosis of the middle cerebral or basilar artery, I doubt that the use of anticoagulants would be of any use. If it is a lesion affecting small branches and follows a criterion of the previous query, anticoagulants should be used for a long period of time, or at least until all symptoms of recurrence have ceased. It is difficult to establish rigid criteria in these cases since there is no definite policy as yet with regard to the use of anticoagulants; certainly from an experimental standpoint we are still not justified in using them in cerebrovascular accidents as they are generally recognized. If we learn to detect the early phases of the "stroke," anticoagulants will be more generally utilized.

Cerebral Embolism and Thrombosis vs. Hemorrhage

Query: In patients with arteriosclerosis can you be sure that an acute cerebrovascular accident is due to thrombosis or embolism and not hemorrhage?

Answer: The law of averages speaks against primary hemorrhage. The most common lesion is a thrombosis, but it is not a solitary lesion. There have usually been multiple insults with involvement of branches of a vessel and, finally, a large lesion in which there is a coalescence of areas of softening with extravasation of blood, which gives the area an hemorrhagic appearance. When hemorrhage occurs, the lesion is usually massive. Frequently the course is rapidly downhill because the hemorrhage breaks into the ventricle with diffusion

of blood throughout the cerebrospinal fluid system. A rapid fulminating course ensues. Embolization usually occurs in the course of diseases that permit emboli so that if an individual has arteriosclerotic heart disease, if fibrillating, he may have emboli. In such instances, the onset is sometimes a convulsion. A cerebrovascular accident may also be acute, mild, and transient with good recovery as in an intermittent vascular insufficiency.

Answers to above queries all by BENJAMIN BOSHES, M.D., Department of Neurology and Psychiatry, Northwestern University, Chicago, Illinois.

Announcements

Cardiovascular Research Training Program

A one-year course intended to provide technical training in basic research methods for cardiovascular studies will begin July 1 at the Medical College of Georgia, Augusta. Known as the Postgraduate Cardiovascular Research and Training Program, it will be under joint sponsorship of the American Heart Association and the National Heart Institute of the U. S. Public Health Service.

Open to graduates holding M.D. or Ph.D. degrees or their equivalent, the program will be conducted under the direction of Dr. W. F. Hamilton, Professor of Physiology, and Dr. R. P. Ahlquist, Professor of Pharmacology. Trainees will be instructed and guided by senior faculty members of the departments of Physiology, Pharmacology, Thoracic Surgery, and Medicine. Applications may be obtained from either Drs. Hamilton or Ahlquist at the Medical College of Georgia.

Dr. Wakerlin Named Medical Director of American Heart Association

Dr. George E. Wakerlin has been appointed Medical Director of the American Heart Association. Dr. Wakerlin comes to the Association from the University of Illinois College of Medicine in Chicago, where he has served as Professor and Head of the Department of Physiology since 1937.

Dr. Wakerlin will be responsible for planning and directing the medical and scientific program of the American Heart Association, filling the post held by the late Dr. Eugene B. Ferris We congratulate Dr. Wakerlin and wish him success in his new undertaking.

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1. Bedell, A. J.: Clin. Symposia 9:135 (Sept.-Oct.) 1957. 2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. 44:456 (March) 1956.

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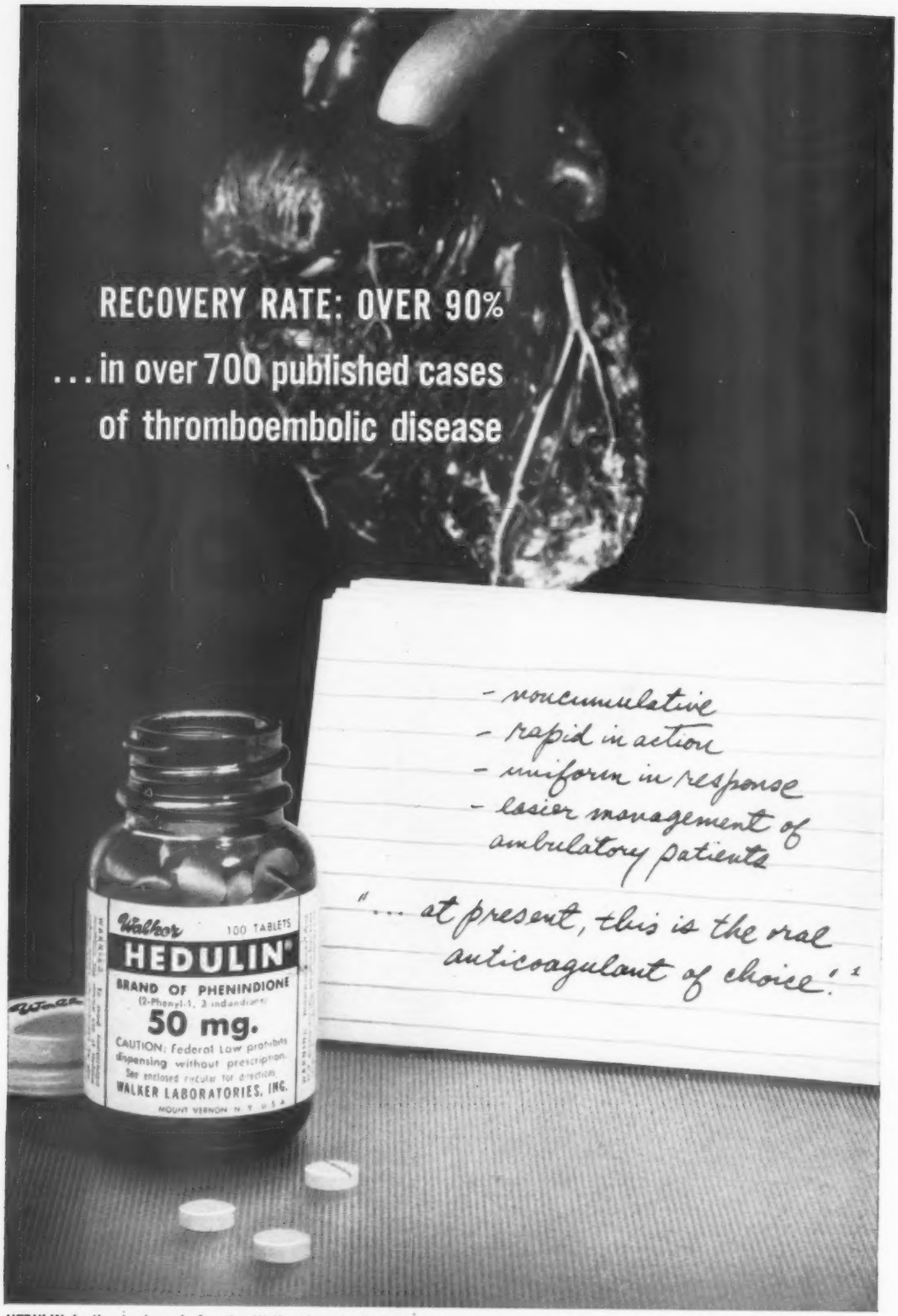
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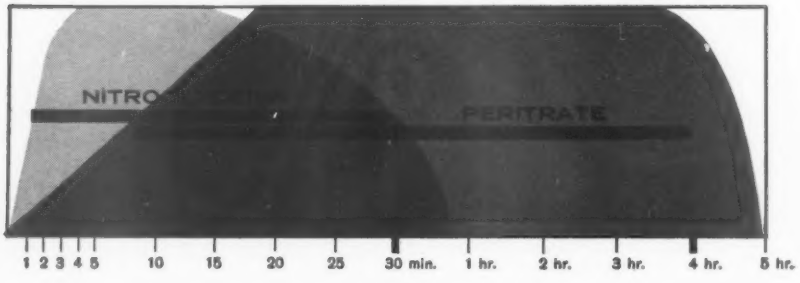

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Use of Radioactive Iodine in the Treatment of Angina Pectoris
Robert L. Segal, Solomon Silver, Stephen B. Yohalem, and Robert A. Newburger 671

Radioactive iodine is useful in the treatment of the incapacitating anginal syndrome which is refractory to standard therapy. The proper selection of patients, methods of treatment, and results in 65 cases are presented. Good to excellent relief of intractable angina was obtained in 60 per cent of the cases. Therapeutic failures resulted from the failure to induce hypothyroidism or the development of adverse side-effects, such as myxedema, toxic effects of radiation, or radiation thyroiditis with paradoxical transient hyperthyroidism. The latter effect can be avoided by initiating the treatment with small fractional doses.

Acute Myocardial Infarction in a City Hospital. I. Clinical Review of 264 Cases
Monte Malach and Benjamin A. Rosenberg 682

This is a meticulous clinical study and analysis of a large series of acute myocardial infarctions observed in a single year in a large city hospital. Despite considerable progress in diagnosis and treatment of this condition, the mortality rate was quite high (45 per cent). This reflected the type of case material in such a hospital ward, with an older average age, lack of private nursing, and high incidence of critically ill patients in shock or heart failure. The authors review the prognostic significance of various predisposing factors and clinical symptoms and signs and compare their findings with those previously reported in the past two decades.

Surgical Treatment for Endocardial Fibroelastosis or Anomalous Left Coronary Artery. Four Years' Experience with Poudrage
Raphael N. Paul and S. Gwin Robbins 694

Primary endocardial fibroelastosis is a serious congenital lesion which should be suspected in infants with lack of weight gain, vomiting, and dyspnea. Characteristic findings are ECG and x-ray evidence of left ventricular hypertrophy and visualization by angiocardiography of a large thick-walled left ventricle with delayed emptying. The prognosis is very poor, most infants dying of heart failure before the age of two years. Accepting the concept that heart failure results from myocardial anoxia and ischemia due to obstruction of drainage by the thickened endocardium, the authors had the ingenious idea of performing cardiopexy with talc in an attempt to stimulate extracardiac collateral circulation. Of their ten cases (including one of anomalous left coronary artery) six have survived for a sufficient period to indicate that a good clinical improvement has occurred. This was judged by disappearance of heart failure despite discontinuance of digitalis, improved weight curve, decreased heart size or C/T ratio and survival to the age of 3 to $3^{3}/_{4}$ years.

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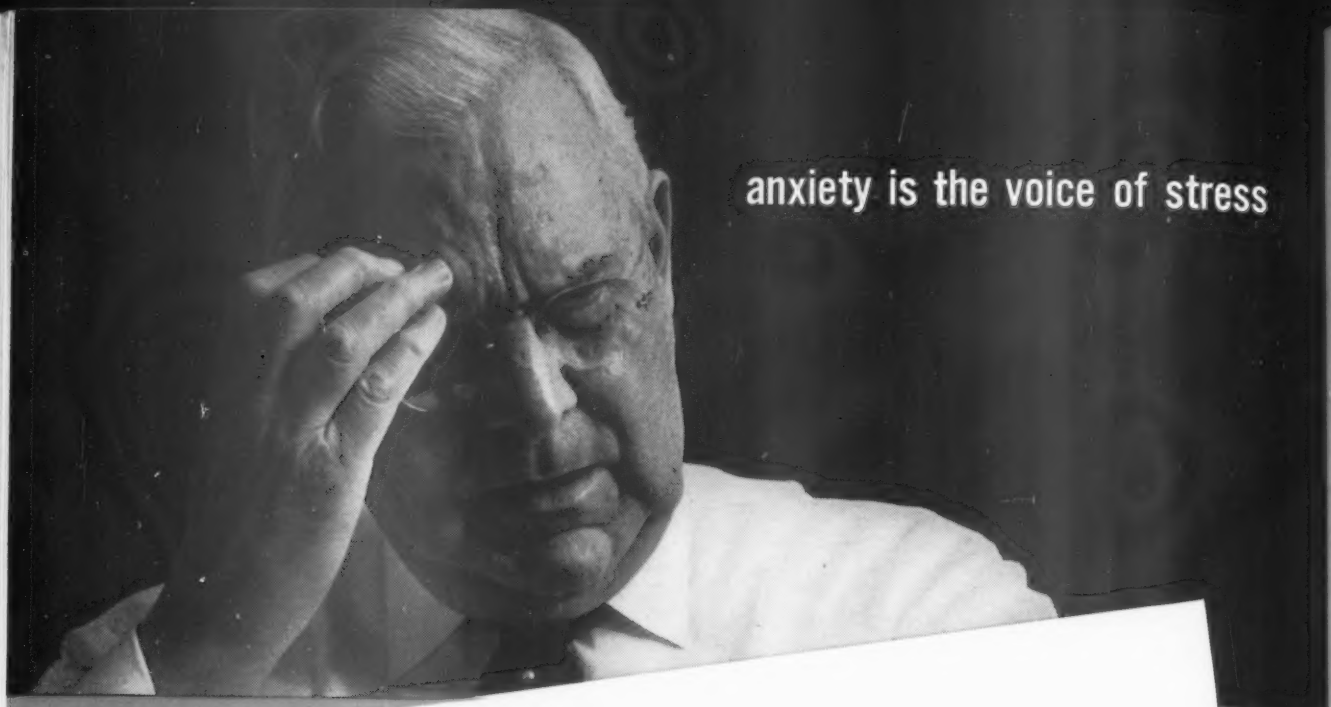

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CHRIST ARAVANIS AND ALDO A. LUISADA 706

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Clinical Evaluation of Acetyl-Digitoxin
JOSEPH B. VACCA, JOSEPH M. SCHUSTER, AND WILLIAM A. KNIGHT, JR. 717

Data in 32 patients digitalized with acetyl-digitoxin indicate that this recently developed cardiac glycoside is effective, quick-acting, and well tolerated in the digitalizing dose of 1.0 to 4.0 mg and a maintenance dose of 0.1 to 0.2 mg daily. The toxic effects which were deliberately produced to determine the proper dosage generally consisted of gastrointestinal symptoms. These generally disappeared promptly on discontinuing the drug.

Clinical Evaluation of Intramuscular Digitoxin in the Management of Congestive Heart Failure
NICHOLAS A. DE FRANCIS, JOSEPH KLEMENTS, AND ARTHUR GORDON 723

There has been a distinct need for a nontoxic, painless and effective digitoxin solution for intramuscular administration. The preparation used in this study fills such a need. It appears to be therapeutically effective with few undesirable local or systemic reactions. The dose for initiating and maintaining digitalization with intramuscular digitoxin was equivalent to the oral or intravenous dose.

Experimental Studies

Force, Work and Power Ballistocardiography
SOON KYU SUH, W. H. COOPER, W. H. FREDERICK, AND E. E. EDDLEMAN, JR. 726

Methods for analyzing ultra-low frequency ballistocardiograms are presented which are based upon standard physical formulae. By recording the velocity and acceleration ballistocardiograms, force, work, and power of the heart can be determined. This approach promises to offer a new use for the ballistocardiogram in studying myocardial function and reserve under the influence of various drugs and physiologic stresses as well as in various heart diseases.

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Aneurysms of the Thoracic Aorta. Review of Diagnostic and Etiologic Features
ISRAEL STEINBERG 736

Advances in cardiovascular surgery make this diagnostic and etiologic review with illustrative angiocardiograms of aneurysms of the thoracic aorta instructive, timely, and important. Although conventional roentgenography and fluoroscopy are valuable in recognition and localization, the definitive diagnosis of

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thoracic aneurysms and differentiation from other conditions is made by angiocardiography. It is also helpful to the surgeon in preoperative delineation of the extent of the aneurysm. Helpful clues are presented in differentiating syphilitic, rheumatic, arteriosclerotic, traumatic, and congenital aneurysms. Of particular interest are the findings in aneurysm of the aortic sinuses of Valsalva with or without rupture into the right atrium.

Report on Therapy

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BURTON M. COHEN 748

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CRAWFORD W. ADAMS AND GERALD EDER 765

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RUDOLF A. COLMERS 768

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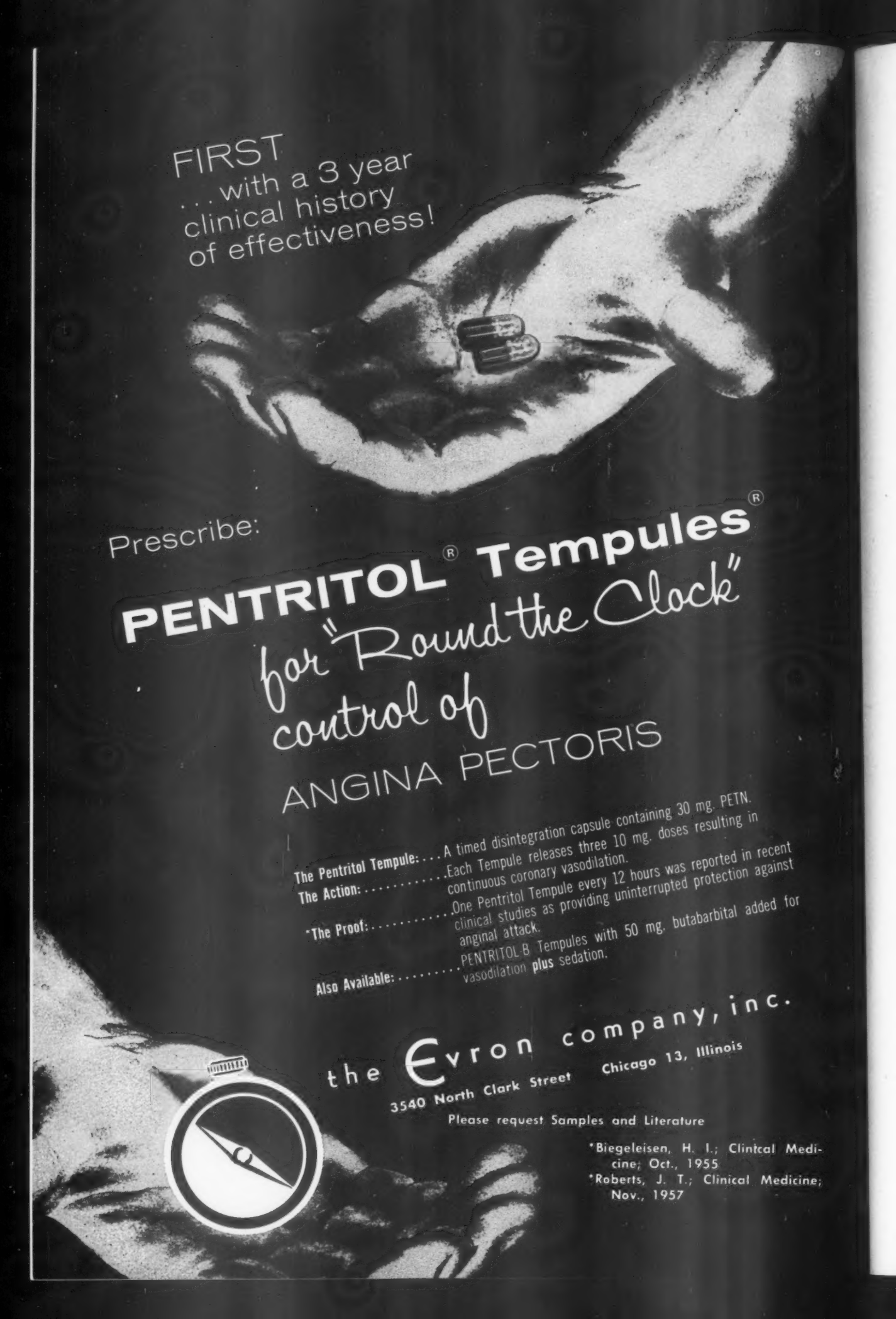
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*Biegeleisen, H. I.; Clinical Medicine; Oct., 1955
*Roberts, J. T.; Clinical Medicine; Nov., 1957

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Historical Milestones

Excerpts from a Lecture by Carl Gerhardt on Haemorrhagic Infarction of the Lungs (1875) . . . . . SAUL JARCHO 774

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When paroxysmal tachycardia occurs in a patient with hypertensive or coronary heart disease, the ensuing coronary insufficiency may lead to acute myocardial ischemia. The latter may produce clinical signs and symptoms and electrocardiographic changes which simulate those of myocardial infarction. Reflex vagal stimulation by eyeball or carotid sinus pressure may slow the heart abruptly and revert the rhythm to normal. In the case under consideration this maneuver abolished the myocardial ischemia and allowed proper interpretation of the electrocardiogram to exclude myocardial infarction.

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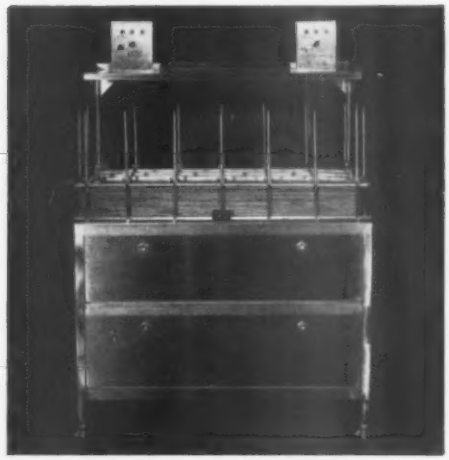

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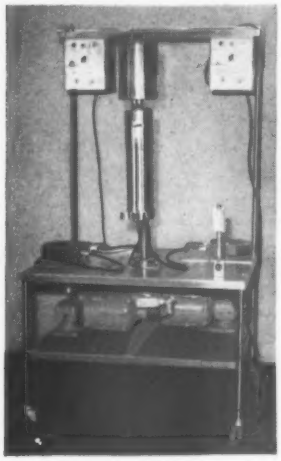

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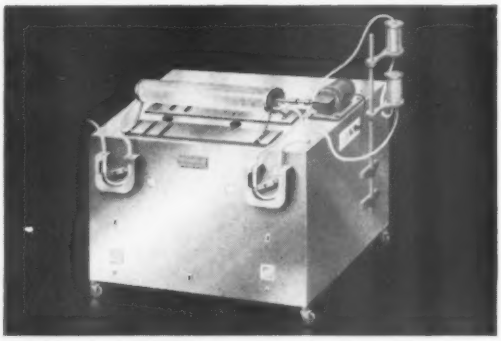

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1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956.

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1. Ensor, R. E. and H. R. Peters, *Ann. Int. Med.*, 47:731, 1957.

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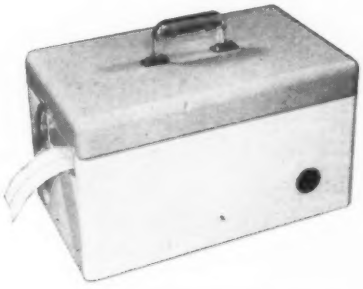

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*Feinblatt, T.M. and Ferguson, E.A.: New Eng. J. of Med. (Feb. 21) 1957.

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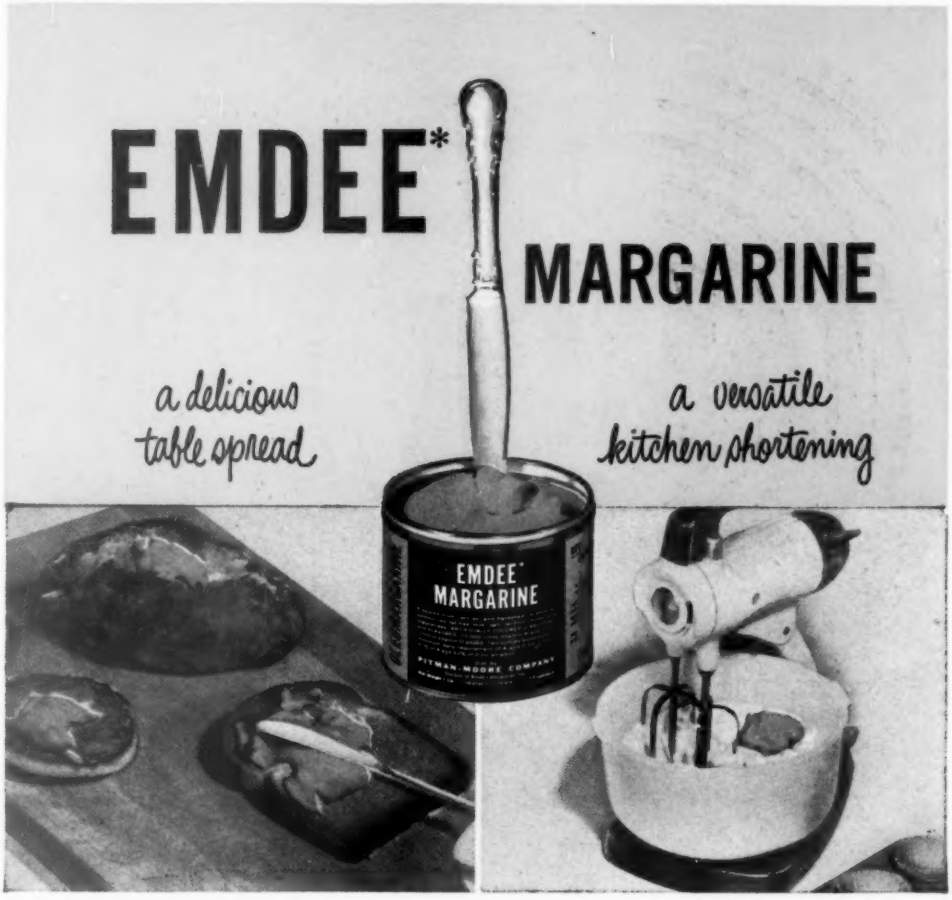

its high corn oil content will not elevate blood cholesterol levels

In Emdee Margarine, 80% of the fat content consists of nonhydrogenated corn oil which has been specially processed to preserve its original content of unsaturated fatty acids. Each 100 Gm. provides 34 Gm. of linoleic acid and 18 Gm. of other unsaturated fatty acids.

Daily use of Emdee Margarine instead of customary table spreads and cooking fats puts a safety factor in the diet... assures patient acceptance... provides a liberal intake of the *unsaturated* fatty acids believed essential in metabolism and important in control of blood cholesterol levels.

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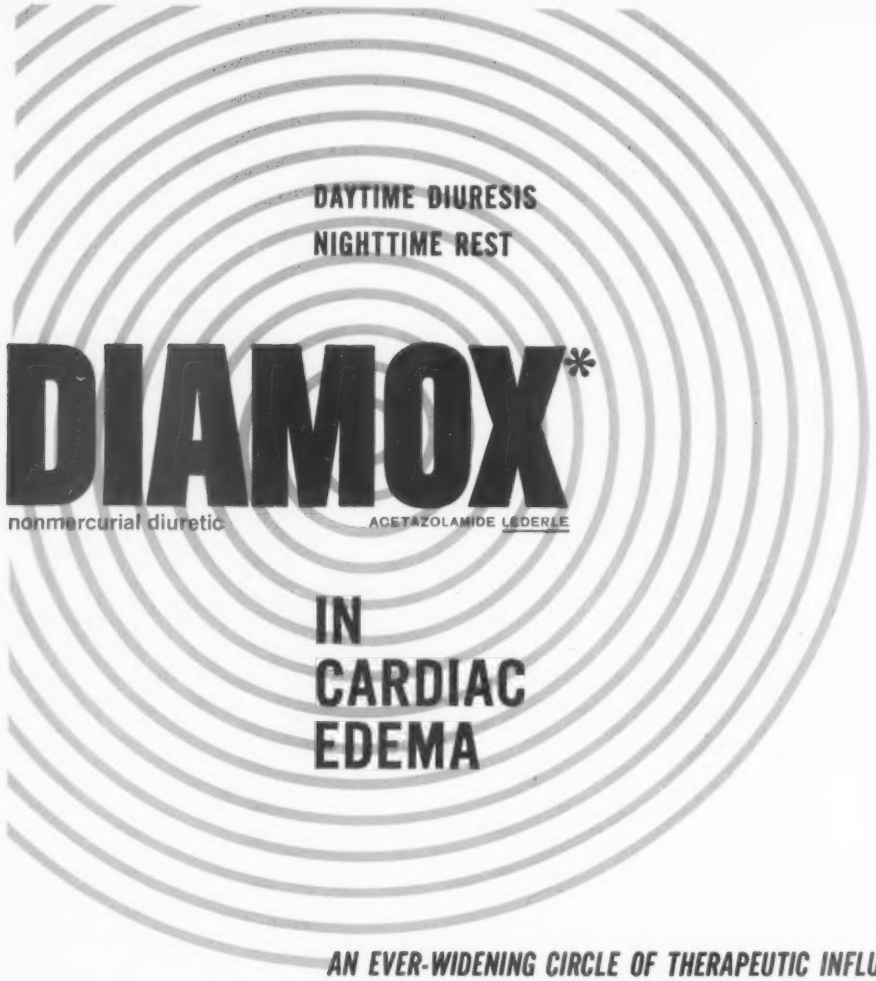

AN EVER-WIDENING CIRCLE OF THERAPEUTIC INFLUENCE

In the treatment of 21 ambulatory patients with edema secondary to congestive heart failure, DIAMOX was substituted for parenteral mercurial diuretic therapy. Only one DIAMOX tablet every other day—maintained all of these ambulatory cardiac patients at optimal body weight as effectively as had parenteral mercurial agents. The increase in comfort and the reduction in the number of outpatient visits considerably improved the well-being of all patients.

Average weights were generally lower, with less fluctuations. Neither side effects nor significant alteration in plasma electrolyte pattern was noted during the course of treatment which extended to 18 months. Four patients were observed for a short period without any specific diuretic treatment. In each case there was weight gain with return to the edema-free state within 7-10 days after DIAMOX was reinstituted.[1]

A highly versatile diuretic, DIAMOX has proved to be singularly useful in other conditions as well, including acute glaucoma, epilepsy, toxemia and edema of pregnancy, premenstrual tension, and edema associated with obesity.

Supplied: Scored tablets of 250 mg.; Syrup—250 mg. per 5 cc. teaspoonful; Ampuls of 500 mg. for parenteral use.

1 Braveman, W. S.; Dexter, R. S., and Rubin, A. L.: Diamox (Acetazolamide) as an Oral Diuretic in Ambulatory Cardiac Patients. Am. Heart J. 54:284-290, 1957.

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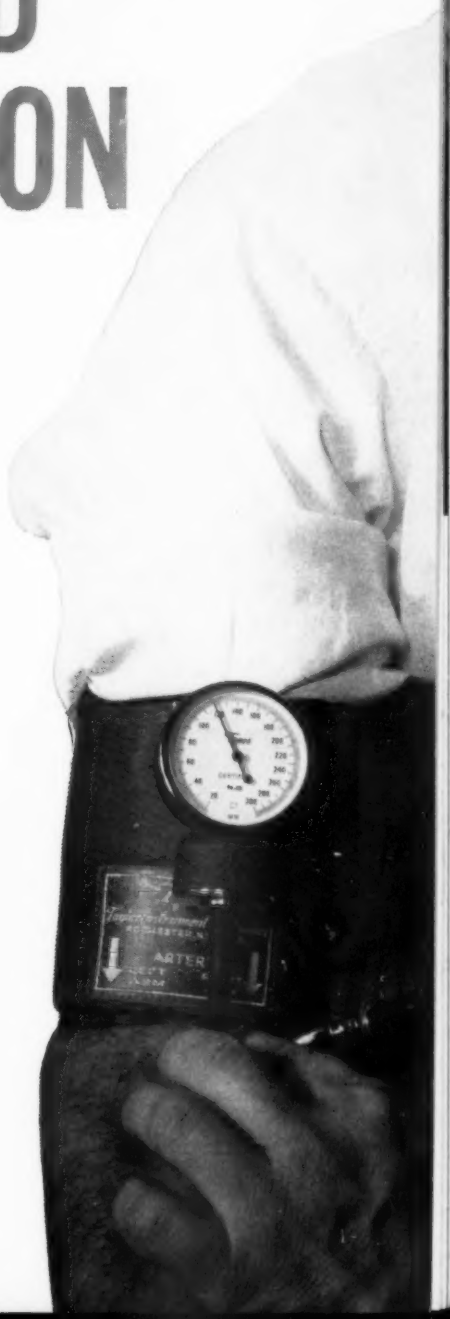
TE · FOR THE CARDIAC CANDIDATE · FOR

CAUGHT BETWEEN HIS TENSION AND HYPERTENSION



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OVERCOMES THE DRAWBACKS OF PREVIOUS RAUWOLFIA AND RESERPINE THERAPY—

the distinctive new rauwolfia alkaloid. Untoward reactions infrequent and minimal. Provides significantly better, uniformly sustained tranquilization and blood pressure reduction in the tension-hypertension syndrome, as well as in acute anxiety states and chronic mental disorders.[1-4]

SUPPLIED: Moderil Tablets—yellow, scored 0.25 mg. oval tablets, bottles of 100 and 500; salmon, scored 0.5 mg. oval tablets, bottles of 100.

1. Moyer, J. H., et al.: South. M. J. 50:499, 1957. 2. Smirk, F. H., and McQueen, E. G.: Lancet 2:119, 1955. 3. Winton, S. S.: Internat. Rec. Med. 170:665, 1957. 4. Malamud, W., et al.: Am. J. Psychiat. 114:193, 1957.

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LINODOXINE*

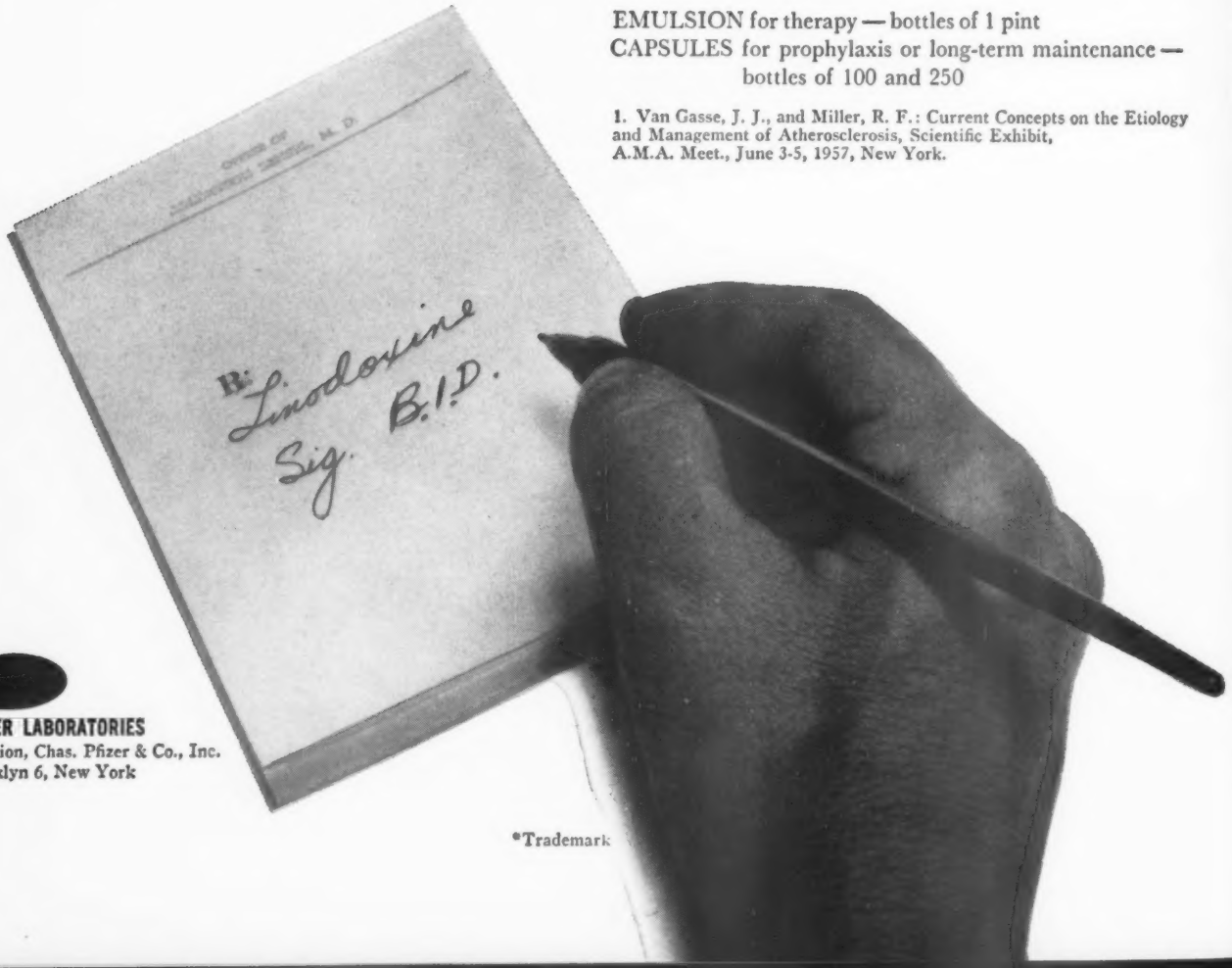
Linoleic Acid (Essential Unsaturated Fatty Acid) and Pyridoxine HCl

lowers elevated serum cholesterol levels[1]

pleasantly orange-flavored emulsion avoids taste fatigue

EMULSION for therapy — bottles of 1 pint
CAPSULES for prophylaxis or long-term maintenance — bottles of 100 and 250

1. Van Gasse, J. J., and Miller, R. F.: Current Concepts on the Etiology and Management of Atherosclerosis, Scientific Exhibit, A.M.A. Meet., June 3-5, 1957, New York.



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simple...safe...effective...

For the alleviation of symptoms in bronchial asthma and the acute episodes of heart failure, CLYSMATHANE (Fleet) supplies prompt therapeutically adequate blood levels of theophylline.[1]

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REFERENCE: (1) Ridolfo, A. S. & Kohlstaedt, K. G., "A simplified method for the rectal instillation of theophylline"—to be published

CLYSMATHANE

(FLEET)

Disposable Rectal Unit

Professional Samples and literature on request

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The completely new portable instrument providing greatly improved performance and versatility not found in any other direct writing electrocardiograph. Small size (5¼" x 10½" x 17") and low weight—20 pounds.

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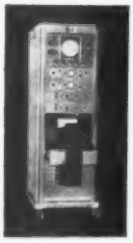

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A string galvanometer instrument . . . the standard of comparison, light in weight and simple to operate. Entire equipment in one mahogany case, 8" x 19" x 10"; weight 30 pounds. May be arranged for heart sound and pulse recording.

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Enables the Doctor to simultaneously HEAR, SEE and permanently RECORD heart sounds. Any portion of the heart sounds may be permanently recorded upon magnetic discs, which may then be played back and viewed at any time. When used in combination with the "Versa-Scribe" or "Simpli-Scribe" Electrocardiograph, the electrocardiogram may be viewed upon the cathode-ray screen of the Recorder while listening to the heart sounds.

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EDUCATIONAL CARDIOSCOPE—For teaching electrocardiography and auscultation by audio-visual demonstration. The EKG, heart sounds and other physiological phenomena may be shown continuously on the 17-inch oscillograph screen. A tape recorder provides a permanent record of heart sounds which may be played back at any time for visual and audio demonstration in lieu of patients.

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A completely integrated, easy-to-use instrument for the determination of such functions as Functional Residual Capacity, Tidal Volume, Vital Capacity, Total Lung Capacity, Total Breathing Capacity, Basal Metabolic Rate, etc.

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Just one year after introduction . . .

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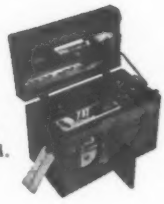
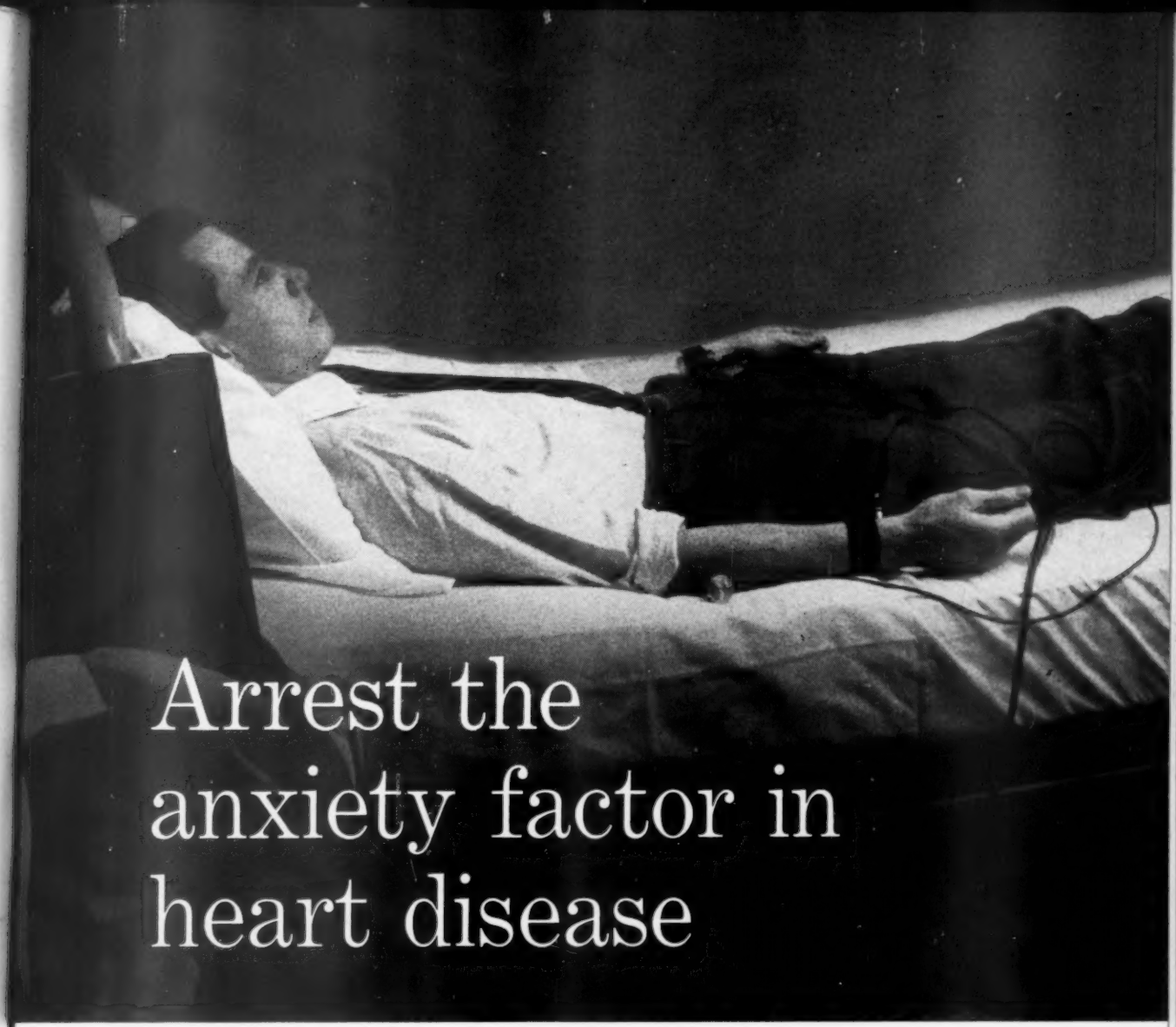


Model 51 Viso-Cardiette, "office standard" in thousands of practices, remains available at $785 delivered, continental U.S.A.



Arrest the anxiety factor in heart disease

without affecting autonomic function

"A cardiac breakdown might be forestalled or arrested" by effective treatment of nervous tension and anxiety.* ■ Adjunctive therapy with meprobamate "definitely reduced nervous tension and anxiety" in all heart patients (80 cases), and enhanced recovery from acute cardiac episodes in many cases.*

*Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.

Because of its unexcelled safety, *Miltown is well suited for tranquilization of chronic heart patients. It is well tolerated, relatively nontoxic, and produces no blood dyscrasias, liver impairment, parkinsonism, or nasal stuffiness. It does not mask toxicity of other drugs.*

Miltown®

Miltown is the original *meprobamate, discovered and introduced by* ® WALLACE LABORATORIES *New Brunswick, N. J.*

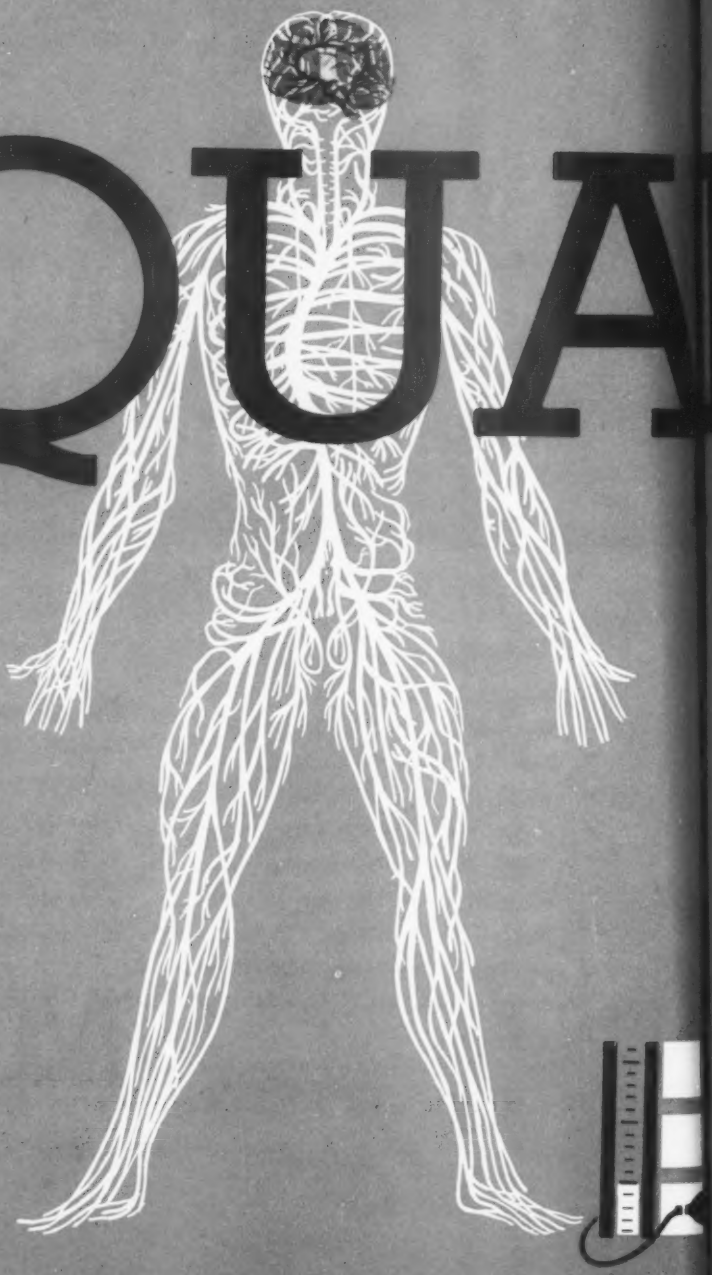
CM-6978

for management

of the hypertensive syndrome—

emotional and vascular

EQUA



Wyeth

Philadelphia 1, Pa.

- **treats the patient and his pressures**
- **achieves and enhances his symptomatic relief**
- **may lessen certain by-effects of ganglionic blockade**

ALYSEN*

Meprobamate and Pentolinium Tartrate, Wyeth

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EQUALYSEN reduces the "tensions" of high blood pressure. It lowers blood pressure, relieves emotional symptoms, and enhances the over-all clinical response. The one preparation provides balanced therapy by the combined use of meprobamate and pentolinium. The pentolinium component returns the pressure toward normal and alleviates manifestations of hypertension. The meprobamate component relaxes emotional and muscular tensions, enhances symptomatic response, and may minimize certain by-effects of ganglionic blockade by reducing necessary dosage of pentolinium. The total benefits have wide significance in antihypertensive management, particularly in elderly patients.[1]

Supplied: Scored tablets, bottles of 50. Each tablet contains 200 mg. of meprobamate (EQUANIL®) and 20 mg. of pentolinium tartrate (ANSOLYSEN® Tartrate).

1. Fulton, L.A., et al.: Am. Pract. & Digest Treat. *8*:1376 (Sept.) 1957.

Perhaps you have withheld tranquilizer therapy from certain cardiac patients, because of fear of undesirable side effects. For this reason, we would like to point out that ATARAX® has been clinically demonstrated to be non-hypotensive and safe.

Anti-arrhythmic action, too: → **48 patients representing 13 different arrhythmias were studied.[1] Only chronic auricular fibrillation was found generally refractory to ATARAX. Follow-up study indicated almost none of this refractory group was responsive to any type of medication.**

ATARAX is effective in 9 out of every 10 tense patients. No major side effects (no parkinsonian effect, no blood dyscrasias) have ever been reported. Prescribe the good-tasting Syrup, compatible with almost any prescription, especially for older patients.

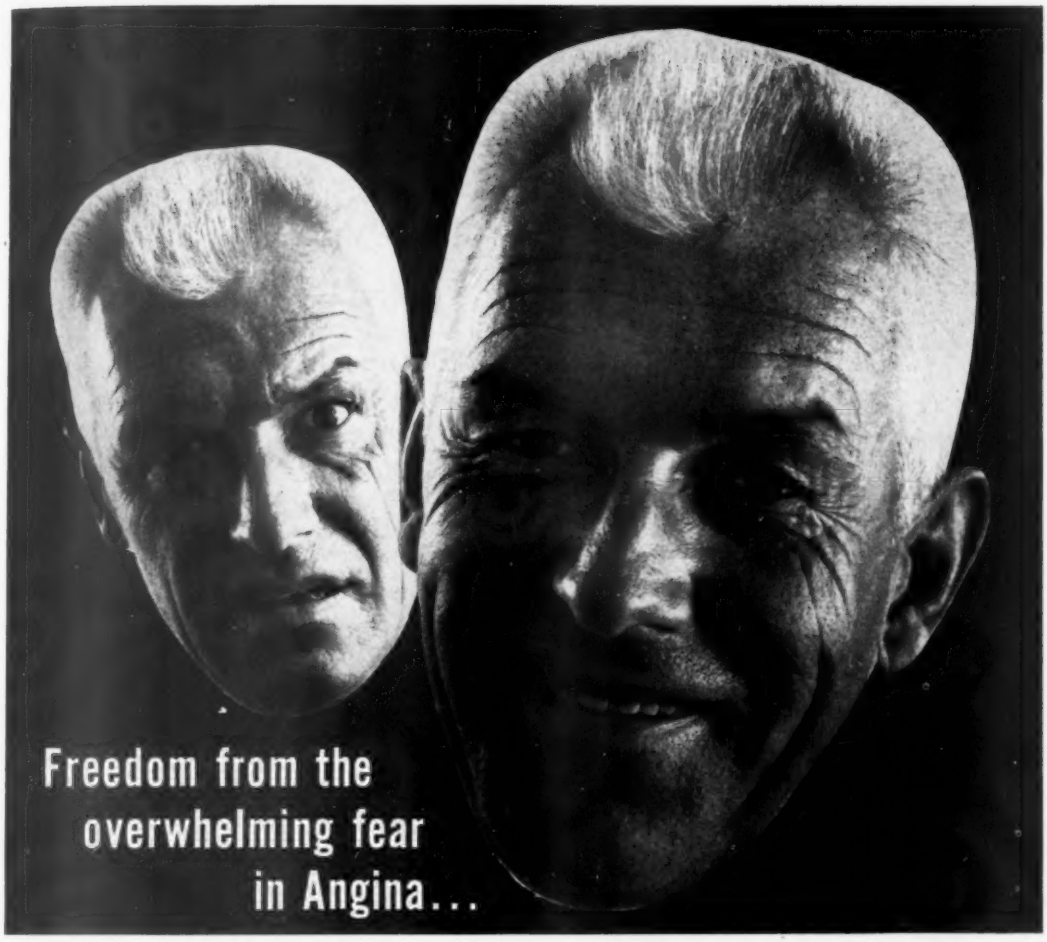
Available in 10 mg., 25 mg. and 100 mg. tablets, bottles of 100. Syrup in pint bottles. Parenteral Solution in 10 cc. multiple-dose vials.

1. Burrell, Z. L., Jr., Gittinger, W. C., and Martinez, A.: Am. J. Cardiology, in press.

ATARAX IN [redacted] INDICATIONS

Roerig

New York 17, New York
Division, Chas. Pfizer & Co., Inc.



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Sustained Action Nitroglycerin Tablets

Around-the-clock protection in Angina Pectoris

Recent clinical studies give impressive evidence of the effectiveness of Nitroglyn as a prophylaxis in the treatment of Angina Pectoris.

1. ..."Reduction of severity, increased exercise tolerance and protection against effort or emotional induction of anginal pain or decubitus angina was accomplished by the use of Nitroglyn in doses of 1/25 to 1/10 grain every 6 to 8 hours, continued indefinitely. Tolerance to Nitroglyn was not observed."

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4. ..."Nitroglyn produces an effect which persists about twenty times as long as the effect of sublingual nitroglycerin."

References:

1. Jablons, Benjamin, M.D. et al; presented at the Inter-American Congress of Cardiology, Havana, Cuba, November 1956.
2. Kutschera, W. and Perger, F., 1st Div. of Medicine in the Vienna City Hospital—Lainz; Ars Medici, Switzerland, May 1957.
3. Huppert, Victor, M.D. and Boyd, Linn J., M.D. F.A.C.P.; Bulletin New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y., May 1956.
4. Mann, Hubert, M.D.; Journal of the Mount Sinai Hospital, New York, N. Y., May-June 1956.

Reprints of above reports available on request.

Literature and samples available to physicians on request . . . write:

KEY CORPORATION, Pharmaceuticals, Miami 37, Florida

Nitroglyn tablets are available in two dosage forms: gr. 1/25th and gr. 1/10th, in bottles of 50 and 500 tablets.

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Unusually Wide Margin of Safety [1-5]—
The average therapeutic dose of Gitaligin is only ⅓ the toxic dose, thus providing a margin of safety approximately twice as great as any other glycoside currently available.

Medium Rate of Dissipation—
rate of excretion between rapidly excreted digoxin and slowly excreted leaf or digitoxin.

Complete Absorption—
rapid and complete from gastrointestinal tract.

Uniform Potency—
constant from batch to batch.

Give all your patients with cardiac decompensation the unique benefits of the "wide safety margin" cardiotonic—

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(White's brand of amorphous gitalin)

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White's

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Supplied:
Gitaligin 0.5 mg. tablets—bottles of 30 and 100.
Gitaligin Injection Ampuls—2.5 mg. in 5 cc. sterile, I.V. solution.
Gitaligin Drops with special calibrated dropper.

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0.5 mg. (1 tablet) of Gitaligin is approximately equivalent to 0.1 Gm. (1½ gr.) digitalis leaf, 0.5 mg. digoxin or 0.1 mg. digitoxin.

1. Harris, R., and Del Giacco, R. R.: Am. Heart J. 52:300 (Aug.) 1956. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. 227:188 (Feb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. 39:1189 (Dec.) 1953. 4. Hejtmancik, M. R., and Herrmann, G. R.: Texas J. M. 51:238 (May) 1955. 5. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation 5:201 (Feb.) 1952.

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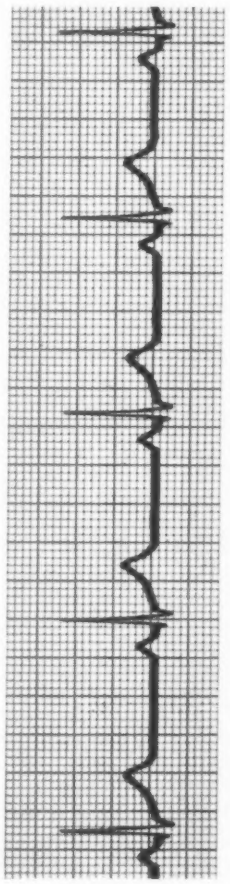
TEN YEARS OF ECG PROGRESS



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Contact the Burdick dealer in your area, or write us for information on our modern line of electrocardiograph equipment.

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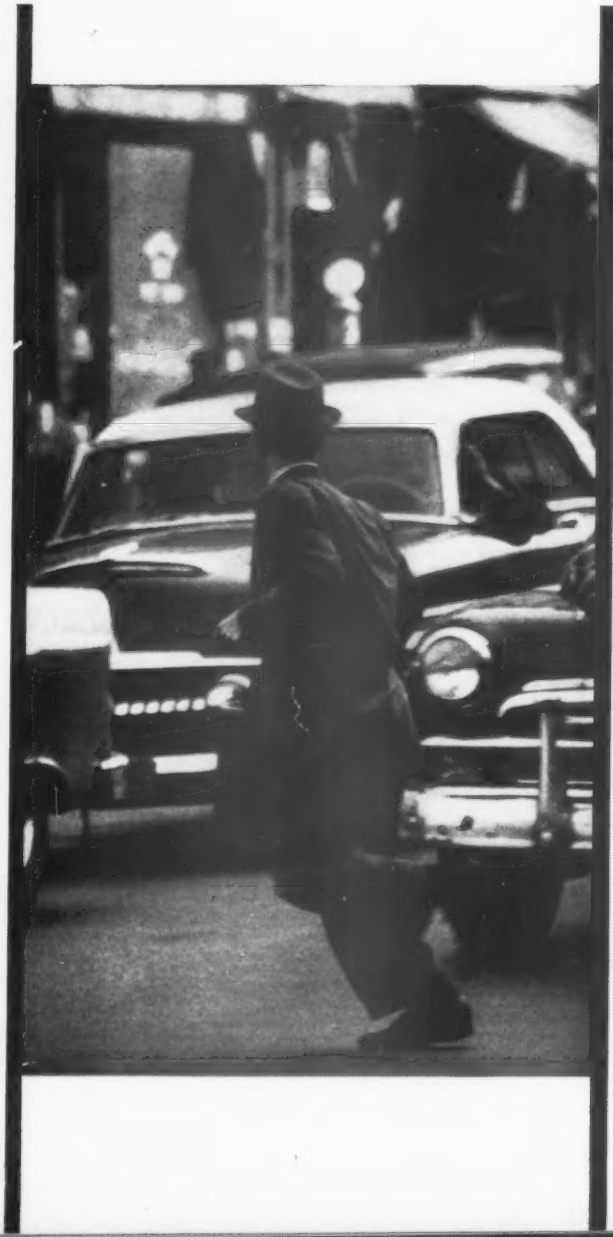
Pentraline

(formerly PENTRAT

for prophylaxis in angina pectori



To insulate your patient against the effects of the eff
and the emotion that may touch off an angina atta
PENTRALINE provides a dual approach to prophyla

The patient can better handle the stress of increa
effort because pentaerythritol tetranitrate is a co
ponent in your prescription. This safe, long-acti
well-tolerated coronary vasodilator improves t
blood flow through the coronary arteries.

And the patient is protected against *emotional fact*
by the reliable sedative action of BUTISOL, combin
with the mild, safe, tranquilizing effect of small do
of reserpine.

Each scored, pink tablet contains:

Pentaerythritol Tetranitrate—10 mg.; BUTISOL SODIU
Butabarbital Sodium—10 mg. (⅙ gr.); Reserpine—0.05 m

Dosage: The usual dosage is one tablet four times a d
administered *before* meals and at bedtime.

Note: PENTRALINE is not intended for treatment of acute attacks
angina pectoris, but rather for routine daily use as a preventi
measure.

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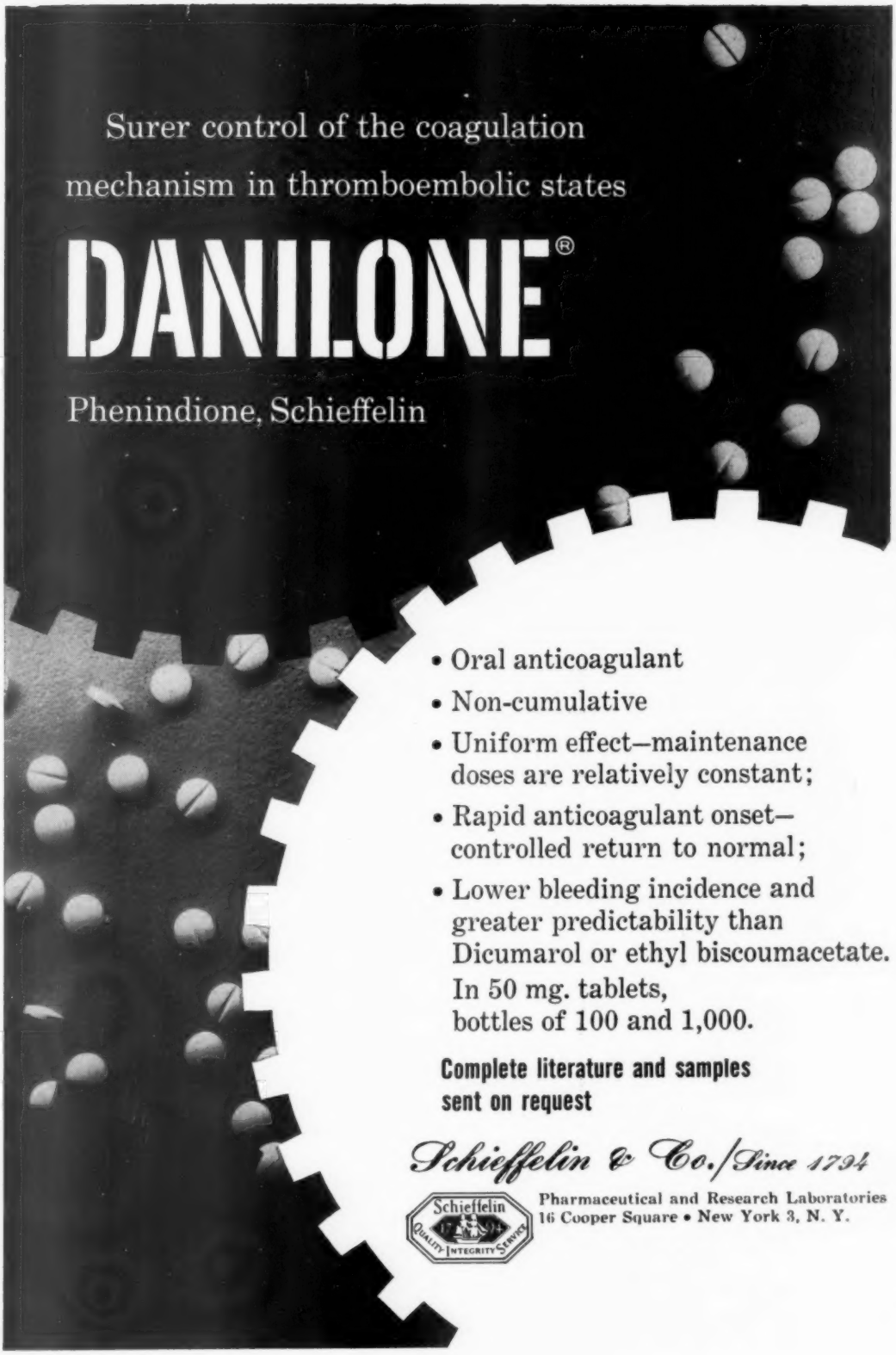
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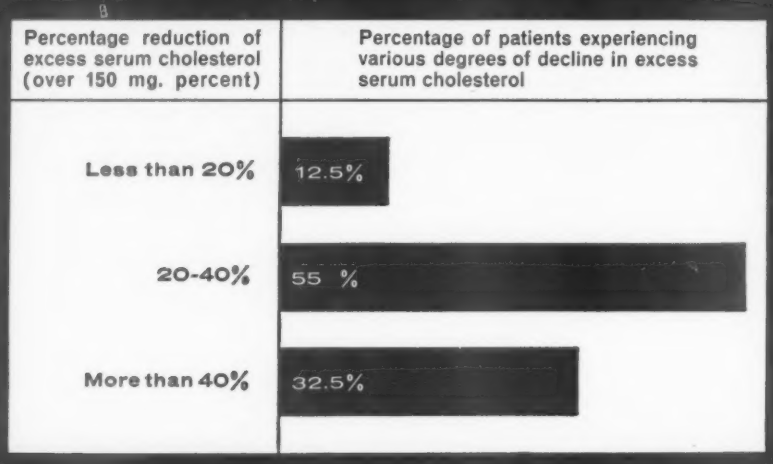
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Less than 20%
12.5%
20-40%
55 %
More than 40%
32.5%

. . . without the necessity of dietary restrictions

'Cytellin' provides the most rational and practical therapy available. Without any dietary adjustments, it lowers elevated serum cholesterol concentrations in most patients.

In a number of studies, every patient who co-operated obtained good results from 'Cytellin' therapy. On the average, a 34 percent reduction of excess serum cholesterol (over 150 mg. percent) has been experienced.

In addition to lowering hypercholesteremia, 'Cytellin' has been reported to effect reductions in C/P ratio, S_f10-100 and S_f12-400 lipoproteins, "atherogenic index," beta lipoproteins, and total lipids.

May we send more complete information and bibliography?

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One tablet q. 12 h. to prevent angina pectoris

Provides full 24-hour protection for 8 out of 10 angina patients: In rigorous clinical trials,[1] METAMINE SUSTAINED improved 80 (78%) of 103 patients with angina pectoris, including a group refractory to other medication.

Each METAMINE SUSTAINED tablet slowly releases 10 mg. of METAMINE, the unique, amino nitrate, to provide lasting, 12-hour protection from attacks of angina pectoris.

Simplified dosage—just 1 tablet on arising, and 1 before the evening meal.

Greater economy for your patient with angina pectoris.

Supplied: METAMINE SUSTAINED, 10 mg., bottles of 50 sustained-release tablets. Also available: METAMINE, 2 mg., in bottles of 50 and 500, and METAMINE (2 mg.) with BUTABARBITAL (¼ gr.), bottles of 50 tablets.

[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Medicine and Clinical Therapy, 3:322, October 1956.

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triethanolamine trinitrate biphosphate, LEEMING, 10 mg.
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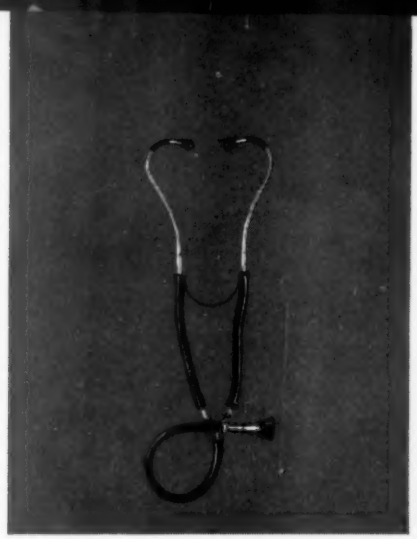

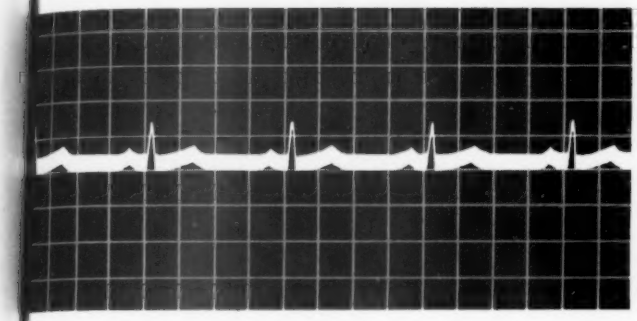

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1. Aravanis, C., and Luisada, A. A.: Am. J. Cardiology, in press.

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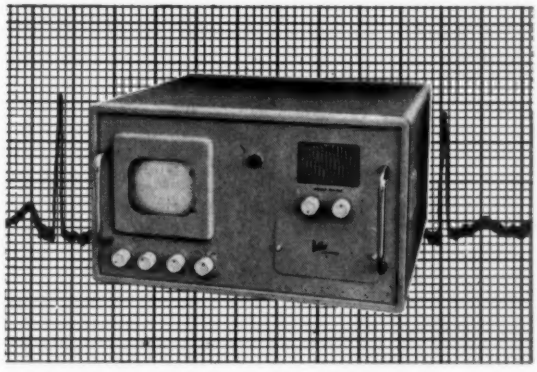

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Riseman, J. E. F., Altman, G. E., and Koretsky, S.: Nitroglycerin and Other Nitrites in the Treatment of Angina Pectoris, Circulation (Jan.) 1958.

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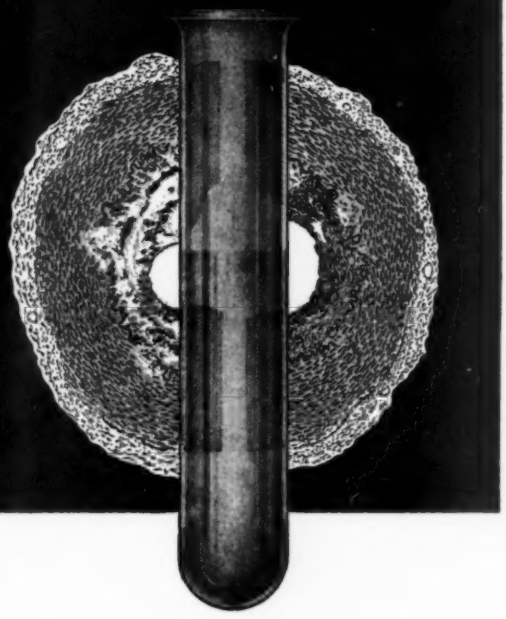
IN DIABETES

Blood Cholesterol Regulation Is Desirable



Frequently, diabetes mellitus is associated with excessive coronary atherosclerosis and heart disease. It is also well recognized that vascular disease manifests itself at an earlier age and progresses more rapidly in the diabetic . . . especially the diabetic female. The early onset and severe degree of atherosclerosis may be due to faulty lipid metabolism, with a concomitant elevation in blood cholesterol levels. Kinsell[1] reports that even in diabetics with extensive vascular disease it is possible to produce normal cholesterol levels with an essential fatty acid emulsion.

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*Ford, R.V., and Moyer, J.H.: Rauwolfia Toxicity in the Treatment of Hypertension, Postgrad. Med. *23*:41 (Jan.) 1958.

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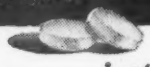

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